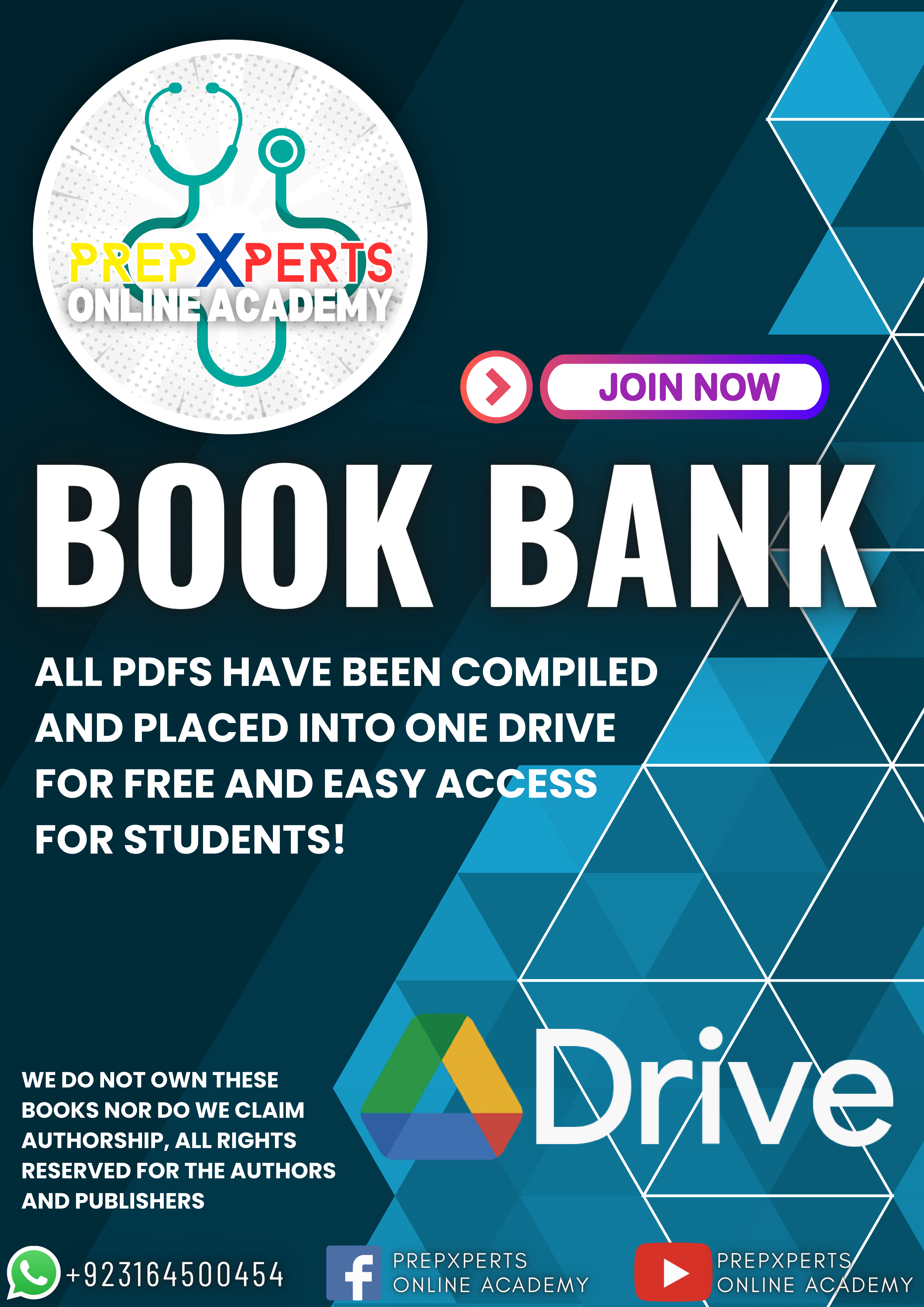
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FOURTH EDITION

RADIANT NOTES

FAST AID

FCPS-1, USMLE-1, PMDC/PMC

by

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- FCPS Pearls has been written to meet the needs and requirements of students appearing in FCPS Part-1 and as well as other medical license exams.
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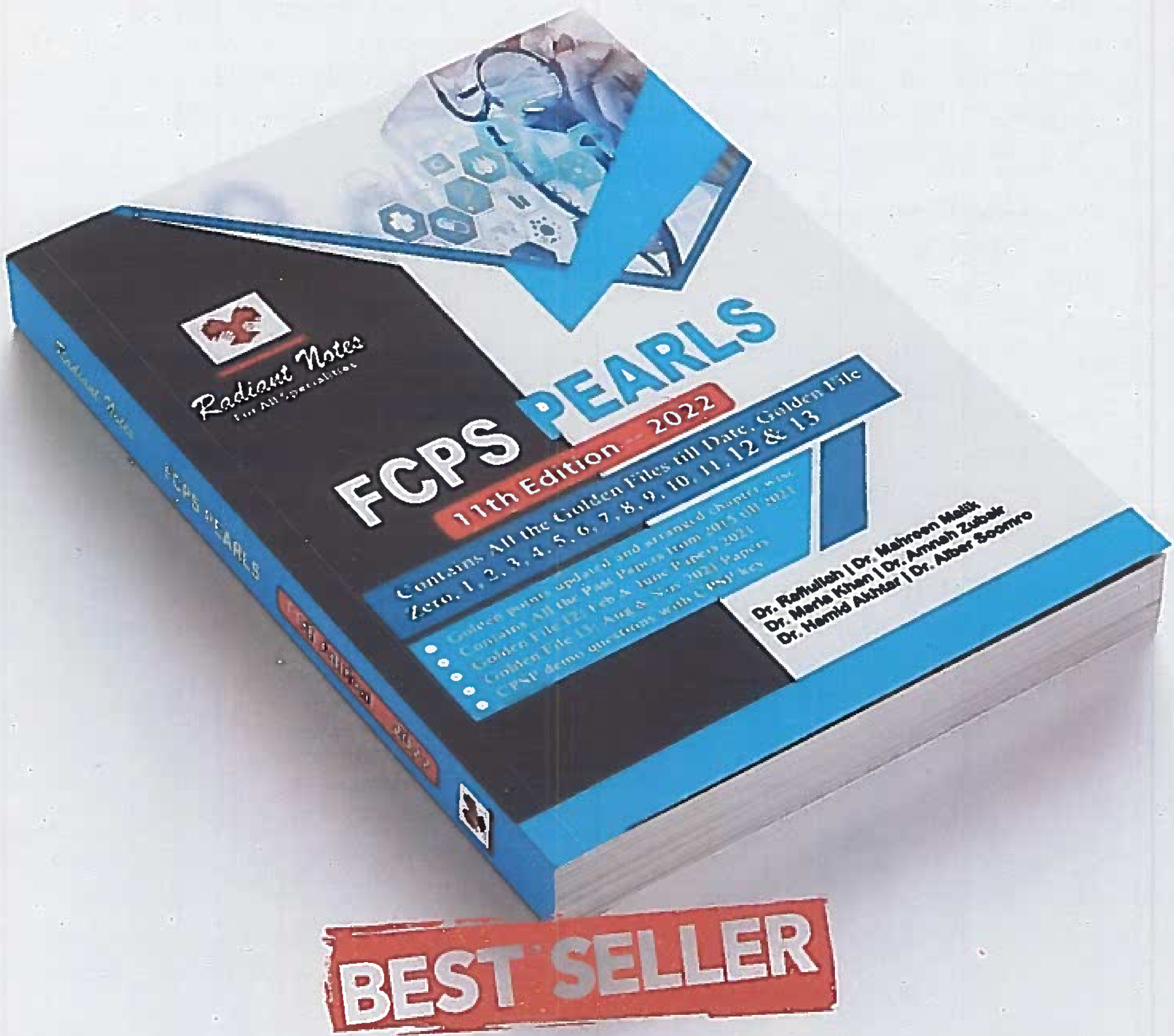


Jaden - Bye

Preface

I am thankful to Almighty Allah who gave me the courage to write this book.

This book is the first ever theory book written for FCPS-1 and so far, the most successful.

Passing FCPS or others license examinations is a difficult milestone for many doctors, but is a mandatory requirement for career progression. Due to busy schedule of Doctors it is almost impossible to go through all the large text books so as to acquire all the knowledge that is required to pass the examinations.

The aim of this book is to provide the busy doctor with a comprehensive review of all the text books

This book will help the students in many ways including

- The book is divided into two sections; Major section from which about 85% of the paper comes and Minor section which covers about 15% of the paper approximately. Neurology chapter has been placed separately with head and neck anatomy for better understanding
- There would be no need to read different books, all the subjects and each and every think will be in this book (will save you the money and time)
- There would be no need to read MCQ's book, EXCEPT PAST PAPERS for practice, as all the MCQ's are already marked, and underlined red and in italic letters (as this line is underlined)
- Given in easy table format, so it could be memorized easily
- Flow charts and mnemonics for easy and quick revision
- Everybody has its own style of learning and pattern of covering syllabus, but if possible follow the same pattern as given in this book as it is for a reason.
- Use this book along with **Radiant notes-FCPS PEARLS** to do all the past papers till date.
- Any suggestions/ corrections would be highly appreciated and his/her name will appear in the future edition.

For which you can contact us at " **doctor_rafi@yahoo.com**
or Contact us on our official Facebook page **"Radiant Notes & Lectures"**

DR. RAFI ULLAH

Note: Anything RED and in *Italic* letters have come in Previous Papers

Contents

MAJOR

MINOR

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS

1

PHYSIOLOGY

Chapter 1: Cell Physiology

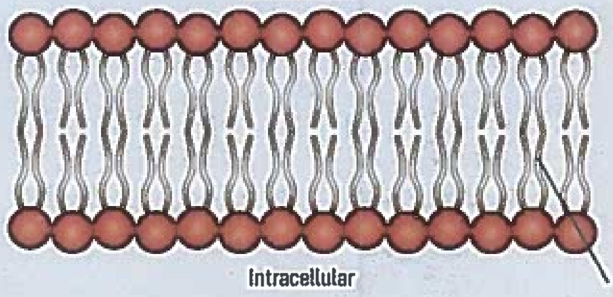
Cell

- Cell is defined as structural and functional unit of body. The entire body contains 100 trillion cells.

Cell Membrane

- **Composition:**
  - Proteins (55%)
  - Lipids (40%)
  - Carbohydrates (5%).

- **Lipid bilayer:**
  - The central lipid layer is a bilayer structure composed of phospholipid molecules.
  - One end of each phospholipid molecule (glycerol backbone) is soluble in water; that is, it is hydrophilic (phosphate end).
  - The other end is soluble only in fats; that is, it is hydrophobic (two fatty acid tails).
  - Lipid layer of the cell membrane is a semipermeable membrane and allows only the fat-soluble substances to pass through it.
  - Thus, the fat-soluble substances like oxygen, carbon dioxide, steroids and alcohol can pass through this lipid layer.
  - The water-soluble substances such as glucose, urea and electrolytes cannot pass through this layer, but may pass through water filled channels or carriers.



Cell Membrane Protein

Integral Proteins	Peripheral Proteins
• They are anchored to and imbedded in cell membrane through hydrophobic interactions. • Provides channels for passage of water-soluble substances.	• Are not imbedded in cell membrane (no covalent bond). But are attached only to one surface of membrane (by electrostatic interactions) or to one end of integral proteins.

Intercellular Junctions

Tight junctions	Gap junctions	Synaptic	Paracrine and autocrine
• Region where the cell membranes of the adjacent cells fuse together firmly. • That prevents the passage of large molecules.	• The intercellular junction that allows passage of ions and smaller molecules between the cells e.g. in heart	• The junction between a nerve fiber and a muscle fiber or between two nerve fibers, through which the signals are transmitted by the release of chemical transmitter.	• By diffusion in interstitial fluid

Cell Organelles

Organelles with limiting membrane	Organelles without limiting membrane
• Endoplasmic reticulum • Golgi apparatus • *Lysosome* • Peroxisome • Centrosome and centrioles • Secretory vesicles • Mitochondria • Nucleus	• Ribosomes • Cytoskeleton

Functions of Cell Organelles

RER	• Synthesis of proteins • Degradation of worn-out organelles • Continuous with nuclear membrane
SER	• Synthesis of lipids and steroids • Storage and metabolism of calcium • Catabolism and detoxification of toxic substances
Ribosomes	• Synthesis of proteins • Basophilia of cell is due to Ribosomes
Golgi apparatus	• Processing, packaging, labelling and delivery of proteins and lipids
Lysosomes	• Arise from Golgi apparatus • Contain hydrolases • Cause degradation of unfolded proteins • Uterus and breast regress after pregnancy by lysosomes • On H & E stain: hollow structure around nuclei
Peroxisomes	• Originate from SER • Contain oxidase, H_2O_2 and catalase • Single membrane, long chain fatty acids oxidation • Catabolism of amino acids and ethanol
Centrosome	• Movement of chromosomes during cell division
Mitochondria	• Energy house of the cell. Self-replicative (contains its own DNA) • Synthesis of ATP • Initiation of apoptosis
Nucleus	• Control of all activities of the cell • Synthesis of RNA • Sending genetic instruction to cytoplasm for protein synthesis • Control of cell division and Storage of hereditary information in genes (DNA)
Nucleolus	• No limiting membrane • Part of nucleus and Site of RNA synthesis
Cytoskeleton	• Shape and Stability of cell shape, Cellular movements • Cytoskeleton which connects ECM to ICM = Intermediate filament • Cytoskeleton connected to ECM = integrin • ECM connected to ICM through = Integrin
Endoplasmic reticulum:	• 2 types ⇨ **Rough ER** (due to attachment of ribosomes) & **Smooth ER** (without ribosomes). • Ribosomes arrange amino acids ⇨ transported to ER, here carbohydrates are added to proteins forming glycoproteins arranged in form of reticular vesicles, which are transported to Golgi apparatus

Transport across Cell Membrane

- Two types: active and passive
- **Passive transport:** transport which does not require metabolic energy, includes diffusion and osmosis
- **Active transport:** transport which require metabolic energy

Diffusion

- Random movement of molecules down their concentration gradient (downhill), and is of two types

Simple Diffusion	Facilitated Diffusion

• Not carrier mediated
• Movement of substances, across cell membrane down an electrochemical gradient (downhill)
• Without any carrier protein
• Caused by simple kinetic motion
  ◦ E.g., O2, Co2.
• Concentration of the diffusing substance increases; the rate of simple diffusion continues to increase proportionately
	• Carrier mediated
	• Movement of substances, across cell membrane down an electrochemical gradient (downhill)
	• Combination with carrier proteins
	• Without utilization of energy is called facilitated diffusion.
	  ◦ E.g., glucose and amino acids.
	• With increase in diffusion substance, in the case of facilitated diffusion, the rate of diffusion cannot rise greater than the Vmax level

Osmosis

Definition	• It is defined as the movement of water (or any other solvent) from low solute concentration to higher solute concentration, through a semipermeable membrane.
Colloid osmotic pressure or oncotic pressure	• Is the osmotic pressure created by proteins e.g., plasma proteins
Osmolality	• No of osmoles of solute per litre of water is called osmolality

Osmole	• To express the concentration of a solution in terms of numbers of particles, the unit called the osmole is used in place of grams.
	  ◦ One osmole is 1-gram molecular weight of osmotically active solute.
	  ◦ Thus, 180 grams of glucose, which is 1-gram molecular weight of glucose, is equal to 1 osmole of glucose because glucose does not dissociate into ions.
	  ◦ Conversely, if a solute dissociates into two ions, e.g., NaCl 1-gram molecular weight of the solute will become 2 osmoles.

Osmolarity	• Concentration of osmotically active particles in a solution
	  ◦ Osmolarity= g multiply by C
	  ◦ Where g=number of particles in a solution and C- concentration.
	    ▪ E.g., what is the Osmolarity of a 1M NaCl solution
	    ▪ Osmolarity= g× C
	    ▪ =2 Osm/mol ×1M
	    ▪ =2 Osm/L answer

Osmotic pressure	• Pressure required to stop osmosis completely is called osmotic pressure. • Calculate by van't hoff's law • Depends on the concentration of osmotically active particles • Increases when the solute concentration increases

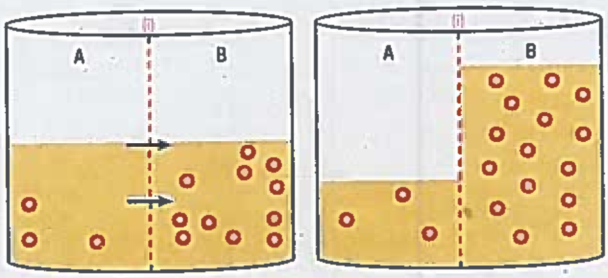


Fig: solute concentration in A-side is low, and solute concentration in B-side is high, so water will move from low solute concentration area to higher solute concentration area, this is called osmosis.

Active Transport

- Movement of substances across cell membrane in combination with carrier proteins against concentration gradient (uphill) by utilization of energy is called active transport.

Primary Active Transport

Transport in which the energy is liberated directly from the breakdown of ATP. E.g.,

Na+-K+ ATPase pump or Na+-K+ pump:

- This in cell membrane transports 3 Na+ from intracellular to extracellular fluid and 2 k+ from extracellular to intracellular fluid i.e., 3Na+/2k+
- Specific inhibitors of Na+-K+ pump is cardiac glycoside drugs e.g. digitalis.

Ca2+-ATPase pump:

- Calcium pumps present in cell membrane and are also present in some organelles of the cell such as sarcoplasmic reticulum in the muscle and the mitochondria of all the cells.
- These pumps move calcium into the organelles by obtaining energy from ATP.

H+-k+-ATPase or proton pump:

- The hydrogen pumps that are present in two important organs have some functional significance.
- Stomach: Hydrogen pumps in parietal cells of the gastric glands are involved in the formation of hydrochloric acid
- Kidney: Hydrogen pumps in epithelial cells of distal convoluted tubules and collecting ducts are involved in the secretion of hydrogen ions from blood into urine.
- It is inhibited by proton pump inhibitors such as omeprazole.

Secondary Active Transport

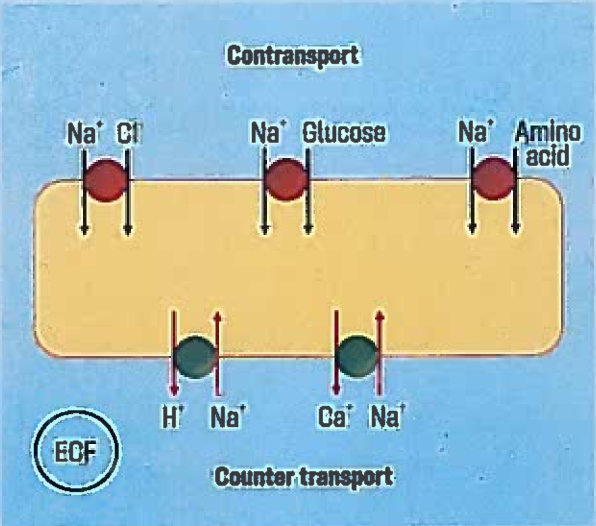
In secondary active transport energy is not provided by ATP, but it is provided by concentration gradient. One solute move (usually Na+) downhill providing energy for the other solute, either in same direction (co-transport) or opposite direction (counter-transport) e.g.,

Na+-glucose co-transport or symport:

- If the solutes move in the same direction across the cell membrane, it is called Cotransport or symport.
- Glucose is transported "uphill"; Na+ is transported "downhill."
- Energy is derived from the "downhill" movement of Na+.

Na+ - Ca+ counter transport:

- Ca moves uphill while Na moves in opposite direction (downhill) providing energy.
- In this process substance is transported in exchange of sodium ions.



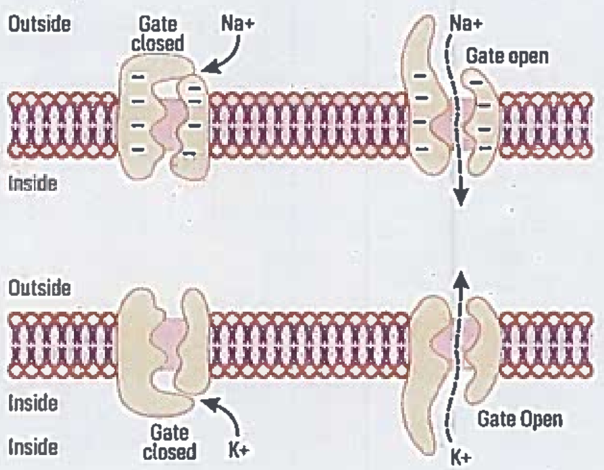
Ion Channels or Protein Channels

- Integral protein molecules invaginate into the pores from either surface of the cell membrane.
- These pores form the channels for the diffusion of water, electrolytes and other substances, which cannot pass through the lipid layer.
- Ion channels are selective e.g., Na+ channels the inner surfaces of this channel are strongly negatively charged, so attract Na+ ions much more than any other ion, so it is selective for Na+ ions.
- Ion channels may be open or closed, the opening and closing of gates are controlled in two principal ways.

1. **Voltage-Gated Channels:**

- Voltage-gated channels are the channels which open whenever there is a change in the membrane potential
- For Na+, gates are present on outside of membrane.
- For k+, gates are present on inside of membrane.

Na+ channels	• When there is a strong negative charge on the inside of the cell membrane ◦ This presumably could cause the outside sodium gates to remain tightly closed. • Conversely, when the inside of the membrane loses its negative charge ◦ These gates would open suddenly and allow tremendous quantities of sodium to pass inward through the sodium pores. • This is the basic mechanism for eliciting action potentials in nerves that are responsible for nerve signals (upstroke of nerve action potential)
K+ channels	• They open when the inside of the cell membrane becomes positively charged. • The opening of these gates is partly responsible for terminating the action potential. (Repolarization of nerve action potential)



2. **Ligand-Gated Channels or Chemical Gating:**

- Ligand-gated channels are the type of channels which open in the presence of some hormonal substances. (hormone=ligand)
- ACh binds with ACh channels and opens it. When opened it is permeable to Na+ and K+ causing depolarization
- This gate is exceedingly important for the transmission of nerve signals from one nerve cell to another.

Diffusion Potential and Equilibrium Potential

- Diffusion potential is the potential across a permeable membrane due to concentration difference of ions, due to which diffusion of ions will occur
- Equilibrium potential is the potential that would balance difference, and would oppose the diffusion.

Membrane Potential

- Electrical potential across cell membrane is called membrane potential
  - Under resting condition outside is +ive and inside is –ive (proteins, organic phosphate compounds and sulfates cannot diffuse out of cell so they cause negativity inside cell membrane)
  - During activity or action potential outside becomes -ive and inside +I've

Resting Membrane Potential

- Membrane potential of nerve fiber when it is not transmitting signals or in resting condition is called RMP. (value= -70mV on inside)
- Contribution by Na+-K+ electrogenic pump
  - Na+-K+ electrogenic pump transports 3 Na+ ions to exterior while 2k+ ions to interior thereby creating negativity inside cell membrane

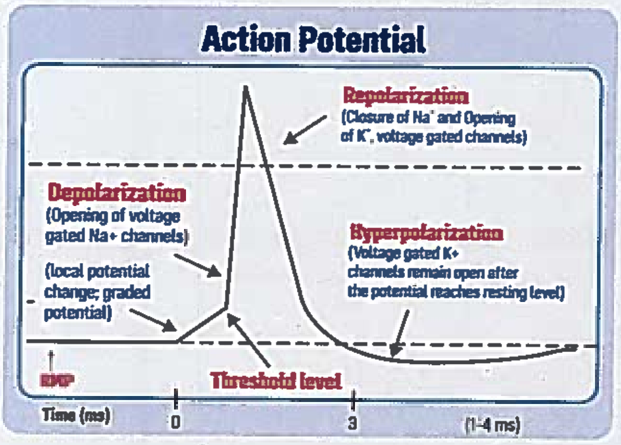
Nernst Potential

- Potential difference across cell membrane that can block further diffusion of an ion completely towards concentration gradient is called Nernst potential of that ion.
- It is used to calculate equilibrium potential.
- Sign is +ive for –ve ions and vice versa.

Action Potential

- Transport of ions across cell membrane due to a stimulus to change membrane potential from normal -ive value to +ive value and then back to –ive value giving rise to an impulse is called action potential.
- **Stages of action potential:**

Resting stage (RMP) = -70 mV	
Depolarization	Due to Na+ influx (inward current) through voltage gated Na+ *channels.* Depolarization makes the membrane potential less negative
Repolarization	It is due to K+ outflux through voltage gated k+ channels. Repolarization makes the membrane potential more negative
Hyperpolarization	After action potential is over, K+ channels remain open, membrane potential becomes close to the k+ equilibrium
Threshold	Is the membrane potential at which action potential becomes unavoidable
All or none response	At threshold potential, net inward current becomes larger than net outward current giving rise to action potential. If net inward current less than outward current=no action potential will occur
Conduction velocity is increased	**By Increase fiber size:** o ↑ *diameter* → ↓ *internal resistance* → ↑ *conduction velocity* **By Myelination.**



Refractory Periodv

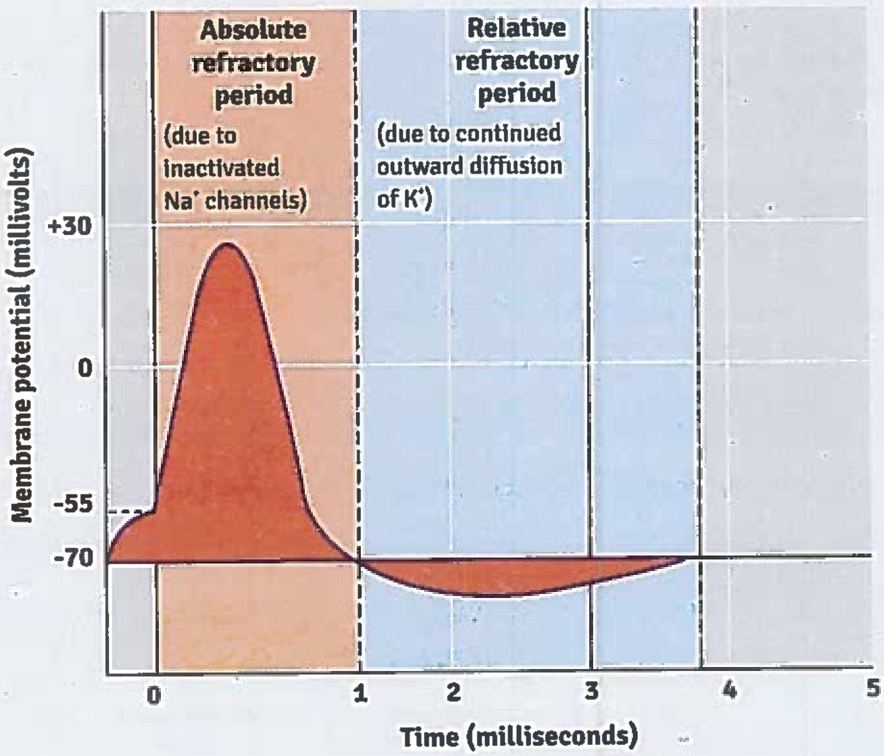
- Period during which a second action potential cannot occur in presence of first action potential is called refractory period

Absolute Refractory Period

- Period during which a second action potential cannot be elicited even with a very strong stimulus is called absolute refractory period.
- Cause: shortly after Na+ channels are opened to cause depolarization they become inactivated and cannot be reopened to cause another depolarization by any amount of stimuli. E.g. during depolarization

Relative Refractory Period

- Period during which stronger than normal stimuli can cause a second action potential.
- Cause: most of Na channels have been reversed from their state of inactivation e.g. during repolarization.



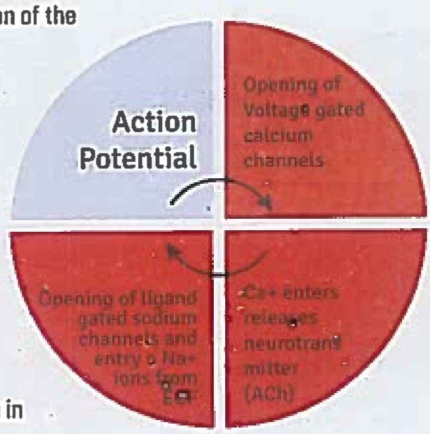
Quick Summary

Depolarization	Due to Na+ influx
Repolarization	Due to K+ outflux
Hyperpolarization	After action potential is over, K+ channels remain open, membrane potential becomes close to the k+ equilibrium
Resting membrane potential	Achieved by = K efflux while maintained by = N-K ATPase Pump

Neuromuscular and Synaptic Transmission

Synapses

- Junction between excitable cells that allows transmission of a signal from first cell to next is called synapse. e.g. neuromuscular junction
- Neuromuscular junction:
  - Synapse between nerve ending (axons) and muscle membrane is called NM junction.
  - The neurotransmitter released from the presynaptic terminal is Ach, and the postsynaptic membrane contains a nicotinic receptor.
  - Axon terminal contains mitochondria and synaptic vesicles. Synaptic vesicles contain the neurotransmitter substance, acetylcholine (Ach).
  - An action potential in the presynaptic cell causes depolarization of the presynaptic terminal→ Ca++ enters into presynaptic terminal causing release of neurotransmitter into synaptic cleft → neurotransmitter combines with receptors on post synaptic cell membrane causing a change in its permeability to ions and consequently change in action potential as shown in fig



  - Inhibitory neurotransmitters hyperpolarize and excitatory neurotransmitters depolarize the postsynaptic membrane.
  - **End plate potential (EPP)**
    - When ACh gated channels open due to arrival of nerve action potential, sudden influx of Na+ influx into muscle fiber causes membrane potential to rise in +ive direction this is called end plate potential.
    - EPP is not an action potential, but initiate and propagate action potential.
    - Under resting condition occasion ACh vesicles fuse with membrane and release small amounts of ACh that causes a small potential called miniature end plate potential (MEEP).
    - MEEP summate to produce full-fledged EPP.

- The ACh is degrade by ACh-esterase (AChE) enzyme to acetyl co-A and choline.
- One half of choline is taken back into presynaptic ending by Na+ choline cotransport and used to synthesize new Ach.
- Neostigmine is AChE inhibitor. Thus prolong EPP.

Myasthenia Gravis

- Autoimmune disease caused by the presence of antibodies to ACh receptors→ reduced ACh → EPP reduced → no action potential → muscle weakness or paralysis.
- Treatment is with neostigmine. (Other drugs include physostigmine and diisopropyl fluorophosphates). Prolongs and enhances the action of Ach

Synthesis of catecholamine's

- Tyrosine $\xrightarrow{\text{tyrosine hydroxylase}}$ L-dopa $\xrightarrow{\text{Dopa decarboxylase}}$ Dopamine $\xrightarrow{\text{doapmine } \beta\text{ - hydroxylase}}$ Nor-epinephrine $\xrightarrow{\text{phenylethanolamine -N-methyltransferase (adrenal medulla)}}$ Epinephrine

Neurotransmitters

Excitatory Neurotransmitters

- Catecholamine's include dopamine, epinephrine and norepinephrine

Norepinephrine	• Synthesized in Locus ceruleus • Released from postganglionic sympathetic neurons • Metabolized in the presynaptic terminal by monoamine oxidase (MAO) and catechol-O methyltransferase (CoMT). Urinary VMA (metabolite of epinephrine and norepinephrine) is elevated in patients with tumors that secrete catecholamine's (adrenal gland tumor→Pheochromocytoma, and neuroblastoma)
	• Synthesized from norepinephrine in adrenal medulla
Dopamine	• Released from the hypothalamus • Inhibits prolactin secretion that is why called prolactin-inhibiting factor (PIF). • Metabolized by MAO and COMT. • D1 receptors activate adenylate cyclase • D2 receptors inhibit adenylate cyclase via a Gi protein
Glutamate	• Excitatory neurotransmitter in the brain ↑ glutamate→ Alzheimer's disease

Inhibitory Neurotransmitters

Serotonin	• Synthesized in Raphe nucleus • Formed from tryptophan→Is converted to melatonin in the pineal gland ↓ serotonin→ depression
GABA	• Inhibitory and synthesized from glutamate
Glycine	• inhibitory neurotransmitter found primarily in the spinal cord and brain stem
Nitric Oxide	• Inhibitory neurotransmitter in gastrointestinal tract, blood vessels, and the central

Disease associations with neurotransmitters

Diseases	Neurotransmitters
• Parkinson disease	↑ACh,↓dopamine
• Huntington disease	↓ACh,↑dopamine
• Schizophrenia	↑dopamine
• Depression	↓ serotonin, ↓norepinephrine,↓dopamine
• Alzheimer disease	↓ACh

Input to synapses

- The postsynaptic cell integrates excitatory and inhibitory inputs.
- When the sum of the input brings the membrane potential of the postsynaptic cell to threshold, it fires an action potential.

- **Excitatory Postsynaptic Potentials (EPSPS)**
  - Are inputs that depolarize the postsynaptic cell, bringing it closer to threshold and closer to firing an action potential.
  - Are caused by opening of channels that are permeable to Na+ and K+, similar to the ACh channels.
  - Excitatory neurotransmitters include ACh, norepinephrine, epinephrine, dopamine, glutamate, and serotonin

Inhibitory Postsynaptic Potentials (IPSPs)
- Are inputs that hyperpolarize the postsynaptic cell, moving it away from threshold and farther from firing an action potential.
- Are caused by opening Cl− channels
- Inhibitory neurotransmitters are Y-aminobutyric acid (GABA) and glycine

Summation at Synapses

- Spatial summation
  Spatial summation occurs when excitatory potentials from many different presynaptic neurons cause the postsynaptic neuron to reach its threshold and fire.

Temporal summation
- Temporal summation occurs when a single presynaptic neuron fires many times in succession, causing the postsynaptic neuron to reach its threshold and fire

Temporal and Spatial Summation

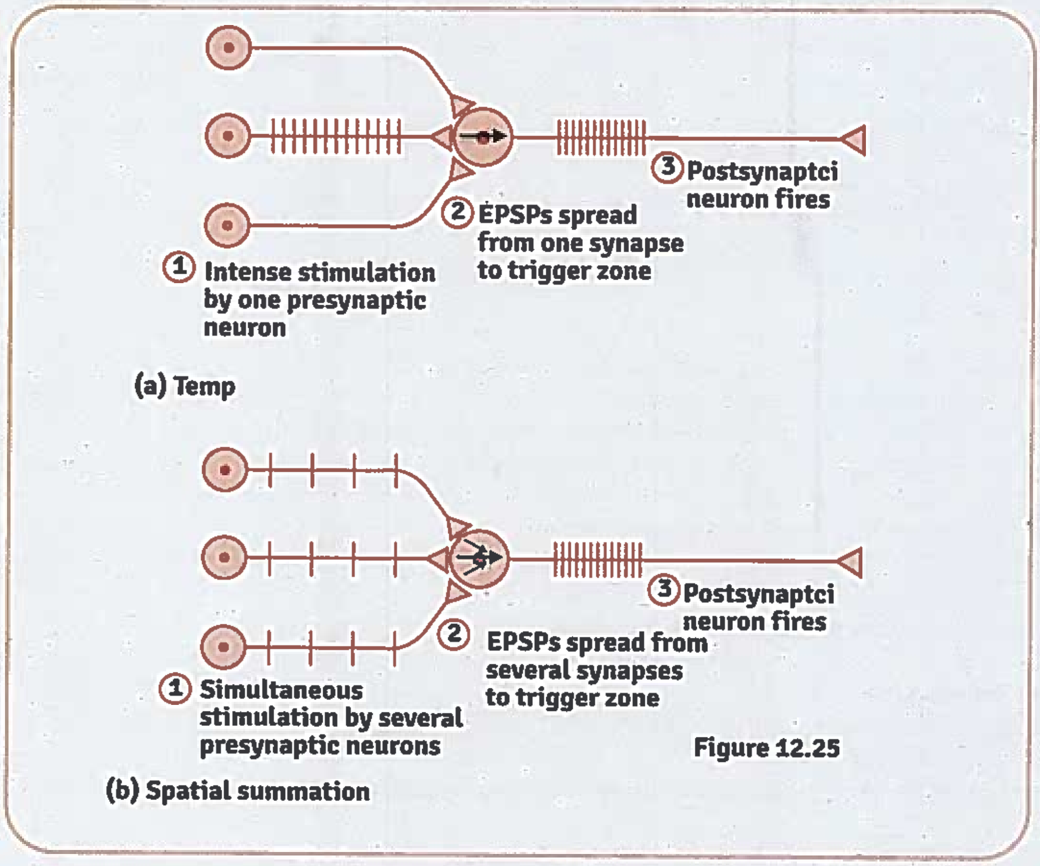


Figure 12.25

Skeletal Muscle

- That type of muscle which is present in skeleton, voluntary in action and striated in appearance is called skeletal muscle
- **Muscle Fiber**
  - Functional and structural unit of muscle is called muscle fiber
  - Composition
    - Sarcolemma ---- It is cell membrane of muscle fiber that surrounds it.
    - Sarcoplasm ----- It is matrix present in muscle fiber.
    - Sarcoplasmic reticulum-- It contains a protein called "calsequestrin", which can bind up to 40 times more Ca++.
    - Nerve ending--- Each muscle fiber is innervated by one nerve ending in centre
    - Myofibrils – Each myofibril contains interdigitating thick and thin filaments arranged longitudinally in sarcomeres.
      - 1500 myosin (thick) filaments.
      - 3000 actin (thin) filaments.

- **Structural Peculiarities In Myofibrils**
  - Actin and myosin filaments partly interdigitate causing alternate dark and light bands.
  - **I BAND:**
    - Light band containing only actin filaments. Isotropic to polarized light
  - **A BAND:**
    - Dark band containing actin and myosin filaments where they overlap.
    - Anisotropic to polarized light
  - **H zone:** Light area in centre of A band seen when muscle is stretched
  - **M Line:** Dark line in centre of H zone.
  - **Z disc:** Z disc passes from myofibril to myofibril and attach them together
  - **Sarcomere:** Portion of myofibril between two successive Z disc is called sarcomere

Thick filaments	Thin filaments
• Are present in the A- band in the centre of the sarcomere.	Are present in the I-bands and anchored at Z lines
• Contain myosin.	C ontain actin, tropomyosin, and troponin
• The myosin heads bind ATP and actin and are involved in cross-bridge formation.	Interdigitate with the thick filaments in a portion of the A band.

Troponin

Is the regulatory protein that permits cross-bridge formation when it binds Ca2+

- Troponin is a complex of three globular proteins:
  - Troponin T ("T" for tropomyosin) attaches the troponin complex to tropomyosin.
  - Troponin I ("I" for inhibition) inhibits the interaction of actin and myosin.
  - Troponin C ("C" for Ca2+) is the Ca2+-binding protein that, when bound to Ca2+, permits the interaction of actin and myosin.

T Tubules:

- Tubular network, conducts action potential from sarcolemma to interior of muscle fiber

Sarcoplasmic Reticulum (SR)

- Is the internal tubular structure that is the site of Ca2+ storage and release for excitation-contraction coupling
- Has terminal cisternae that make intimate contact with the T tubules in a triad arrangement.

- Membrane contains Ca^{2+} ATPase (Ca^{2+} pump), which transports Ca^{2+} from intracellular fluid into the SR interior, keeping intracellular [Ca^{2+}] low.
- Contains Ca^{2+} bound loosely to calsequestrin.
- Contains a Ca^{2+} release channel called the ryanodine receptor.

Steps In Excitation-Contraction Coupling In Skeletal Muscle

- Action potentials in the muscle cell membrane initiate depolarization of the T tubules.
- Depolarization of the T tubules causes release of Ca2+ from the SR into the intracellular fluid
- As a result, Intracellular Ca2+ increases.
- Ca2+ binds to troponin C on the thin filaments, causing a conformational change in troponin that moves tropomyosin out of the way. The cross-bridge cycle begins

- **Cross-bridge cycle** (Shown in fig)

1. The myosin head is attached to the actin filament with ADP + Pi.

(Remember: The myosin head is able to bind to the actin because an myosin-binding site is revealed once a calcium molecule binds to the troponin on the actin, causing a conformational change that allows for the myosin-binding site to be revealed and for the myosin head to bind. Thus, calcium regulates muscle contraction)

2. Once the myosin head binds, its "pivots" and a power-stroke is generated Myosin is displaced toward the plus end of actin. There is hydrolysis of AT P to ADP and inorganic phosphate (Pi).
3. As new ATP attaches to the myosin head, Cross bridge detaches

Remember: Thus, ATP is necessary to release the myosin from the actin, which allows for the muscles to relax and then be ready to undergo another cycle of contraction and crossbridge forming.
In rigor mortis, which is a condition that takes place soon after death, the body is no longer making ATP which is why the muscles are incredibly stiff; the myosin heads cannot unbind actin

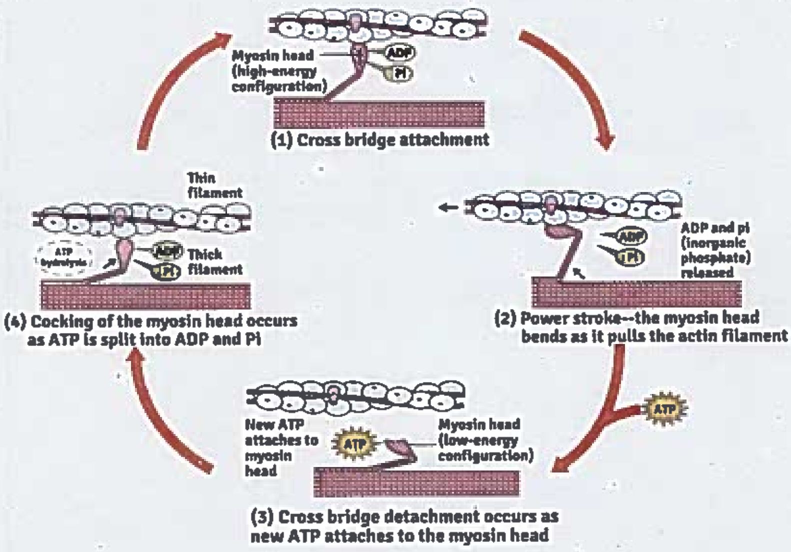
1. ATP hydrolysis will then cause the myosin head to once again "cock" and be in the appropriate conformation to be ready to bind to "myosin-binding site" on the actin filament once again. As you can see, the ATP is now ADP + Pi.

Step-1 again: The myosin head + ADP + Pi once again binds to the actin. The cycle begins.

The cycle repeats as long as Ca2+ is bound to troponin C. Each cross-bridge cycle "walks" myosin further along the actin filament.

- Relaxation occurs when Ca2+ is re-accumulated by the **SR** **C**a2+-**A**TPase (**SERCA**). Intracellular Ca2+ concentration decreases, Ca2+ is released from troponin C, and tropomyosin again blocks the myosin-binding site on actin. As long as intracellular Ca2+ concentration is low, cross-bridge cycling cannot occur.

- Contraction will produce the following:
  - A Band: no change in length.
  - I band and H zone: shortens.



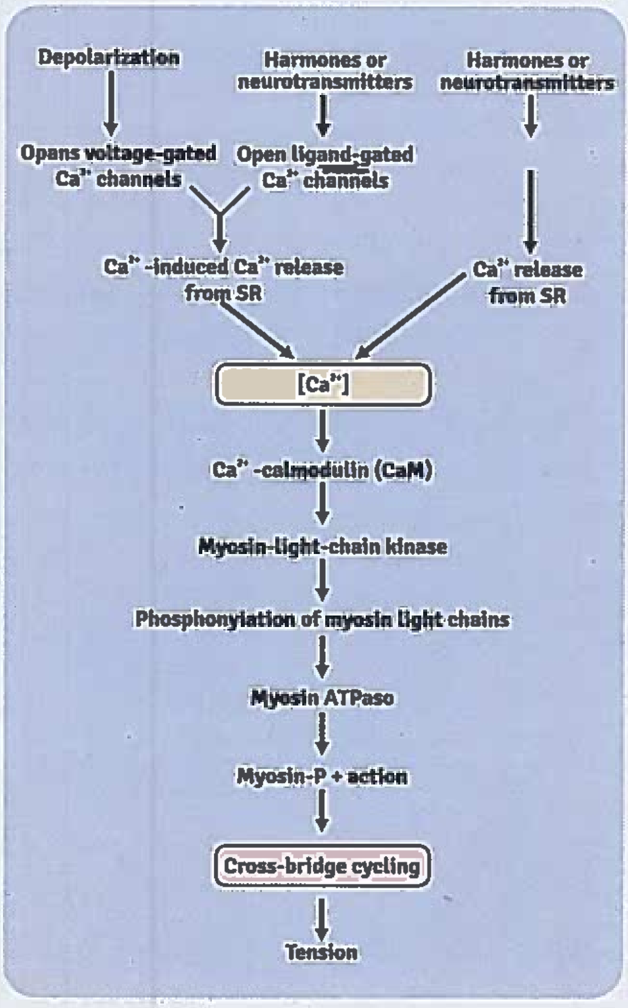
Smooth Muscle

- Has thick and thin filaments that are not arranged in sarcomeres; therefore, they appear homogeneous rather than striated.

Types of Smooth Muscle	
1. Multiunit smooth muscle	• Is present in the iris, ciliary muscle of the lens, and vas deferens. Behaves as separate motor units. Is densely innervated; contraction is controlled by neural innervation (e.g., autonomic nervous system).
2. unitary (singl e-unit/ visceral) smooth muscle	• Most common type Present in the uterus, gastrointestinal tract, ureter, and bladder. Is spontaneously active (exhibits slow waves) and exhibits "pacemaker" activity which is modulated by hormones and neurotransmitters.
3. Vascular smooth muscle	• Has properties of both multiunit and single-unit smooth muscle.

Steps in excitation-contraction coupling in smooth muscle:

- The mechanism of excitation-contraction coupling is different from that in skeletal muscle.
- **There is no troponin; instead, Ca2+ regulates myosin on the thick filaments.**
- Depolarization of the cell membrane opens voltage-gated Ca2+ channels and Ca2+ flows into the cell down its electrochemical gradient, increasing the intracellular [Ca2+].
- Hormones and neurotransmitters may open ligand-gated Ca2+ channels in the cell membrane. ***Ca2+ entering the cell causes release of more Ca2+ from the SR in a process called Ca2+-induced Ca2+ release***. Hormones and neurotransmitters also directly release Ca2+ from the SR through inositol 1, 4, 5-trisphosphate (IP3)-gated Ca2+ channels.
- Intracellular [Ca2+] increases.
- *Ca2+ binds to calmodulin.*
- The Ca2+-calmodulin complex binds to and activates myosin light chain kinase. When activated, myosin light chain kinase phosphorylates myosin and allows it to bind to actin, thus initiating cross-bridge cycling. The amount of tension produced is proportional to the intracellular Ca2+ concentration.
- A decrease in intracellular [Ca2+] produces relaxation.



Muscle and Comparison of Different Types

- Contractile tissue of body is called muscle.
- Types:

Striated Muscle	Unstriated Muscle
• Skeletal muscle (voluntary) • Cardiac muscle (involuntary)	• Smooth muscle (involuntary) present in viscera.

Comparison of Skeletal, Smooth and Cardiac Muscle

Features	Skeletal Muscle	Skeletal Muscle	Smooth Muscle
Appearance	• Striated	• Striated	• Non-striated

Upstroke of action potential	• *Inward Na+ current*	• v<u>in SA node:</u>
		  • *bvia inward Ca2+ current*
		• v<u>in atria, ventricles and purkinje fibers</u>
		  • *via inward Na+ current*
			• *Inward Ca+ current*

Molecular basis for contraction	• Contains troponin-C so forms Ca^{2+}-troponin c	• Ca^{2+}-troponin C	• ***Does not contains troponin instead contains calmodulin so forms Ca^{2+}-calmodulin***
Structure	• Contains T- tubules	• Contains T- tubules	• Lacks T-tubules
Arrangements	• Actin and myosin form sarcomere	• Actin and myosin form sarcomere	• Actin and myosin not organised into sarcomere therefore, they appear homogeneous rather than striated.

Chapter 2: Cardiovascular

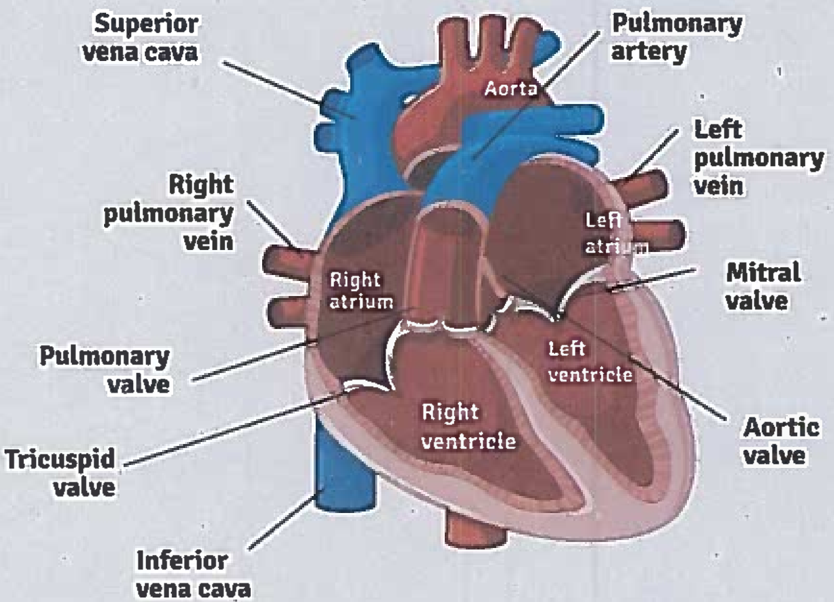
Cardiovascular System Blood Flow

- Cardiac output of the left heart equals cardiac output of the right heart.
  - Cardiac output from the left side of the heart is the systemic blood flow.
  - Cardiac output from the right side of the heart is the pulmonary blood flow

Direction of Blood Flow

- **Systemic Circulation**
  - From the lungs to the left atrium via the pulmonary vein
  - From the left atrium to the left ventricle through the mitral valve
  - From the left ventricle to the aorta through the aortic valve
  - From the aorta to the systemic arteries and the systemic tissues (i.e., cerebral, coronary, renal, splanchnic, skeletal muscle, and skin)
  - From the tissues to the systemic veins and vena cava
  - From the vena cava (mixed venous blood) to the right atrium
  - From the right atrium to the right ventricle through the tricuspid valve

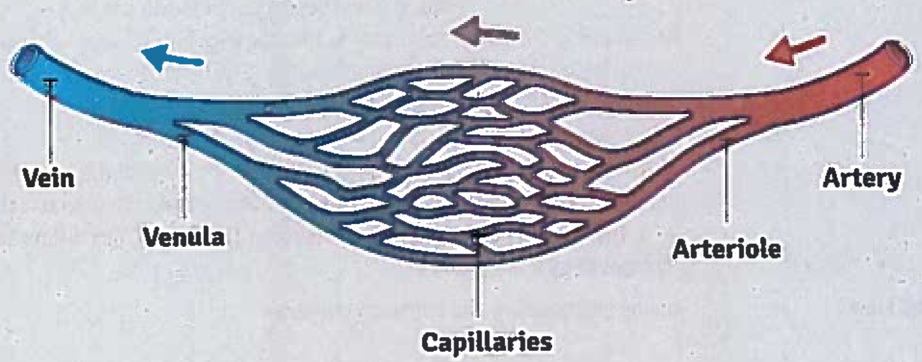
- **Pulmonary Circulation**
  - From the right ventricle to the pulmonary artery through the pulmonic valve
  - From the pulmonary artery to the lungs for oxygenation.



Components of the Vasculature

Arteries	• Arteries are formed by three layers
	  ◦ Outer tunica adventitia
	  ◦ Middle tunica media
	  ◦ Inner tunica intima
	• Are thick walled, under high pressure, Deliver oxygenated blood to the tissues

Arterioles	• Are the smallest branches of the arteries • Are the site of highest resistance in the cardiovascular system • Arteriolar resistance is regulated by the autonomic nervous system (ANS). • $\alpha1$ - Adrenergic receptors are found on the arterioles of the skin, splanchnic, and renal circulations. • $\beta2$ - Adrenergic receptors are found on arterioles of skeletal muscle
Capillaries	• Smallest blood vessel that connects arterioles and venules • Have the largest total cross-sectional and surface area. • Are thin walled and site of exchange of nutrients, water, and gases
Venules	• Are formed from merged capillaries.
Veins	• Carry blood towards heart. • Progressively merge to form larger veins. • The largest vein, the vena cava, returns blood to the heart. • Are thin walled with valves in their lumen. • Are under low pressure. • Contain the highest proportion of the blood in the cardiovascular system. • The blood volume contained in the veins is called the unstressed volume. • Have $\alpha1$-adrenergic receptors.



Volume of Blood in Different Parts of Circulation

- Systemic circulation (84%):
  - Veins (64%)
  - Arteries 13%
  - Arterioles and capillaries 7%.
- Heart 7%
- Pulmonary vessels 9%.

Blood Flow

- Quantity of blood that passes a given point in circulation in given period of time.
- Normal blood flow of adult at rest is 5 L/min.
  - $Q = \frac{\Delta P}{R}$
- Where:
  - Q = flow or cardiac output (mL/min)
  - ΔP = pressure gradient (mm Hg)
  - R = resistance or total peripheral resistance (mm Hg/mL/min)
- Remember:
  - The pressure gradient (ΔP) drives blood flow.
  - Thus, blood flows from high pressure to low pressure.

Laminar Blood Flow	• Blood flows at a steady rate in a straight line (Streamline blood flow).
Turbulent Blood Flow	• Blood flows crosswise in all directions in a vessel • It creates murmurs and more resistance than laminar flow

Reynold's Number	• It is a measure of tendency for turbulence to occur
	• Reynolds' number (and therefore turbulence) is increased by the following factors:
	  ◦ ↓ blood viscosity (e.g., ↓ hematocrit, anemia)
	  ◦ ↑ blood velocity (e.g., narrowing of a vessel)

Resistance	• Expresses by the equation
	  ◦ $R = 8\eta l / \pi r^4$ (Poiseuille's equation)
	  where:
	  ◦ R = resistance
	  ◦ η = viscosity of blood
	  ◦ l = length of blood vessel
	  ◦ r4 = radius of blood vessel to the fourth power
	• Resistance is directly proportional to the viscosity of the blood. For example, increasing viscosity by increasing hematocrit will increase resistance and decrease blood flow.
	• Resistance is directly proportional to the length of the vessel.
	• Resistance is inversely proportional to the fourth power of the vessel radius. This relation- ship is powerful. for example, if blood vessel radius decreases by a factor of 2, then resistance increases by a factor of 16 (2^4), and blood flow accordingly decreases by a factor of 16

Velocity of Blood Flow	• can be expressed by the following equation
	  ◦ V = Q/ A
	  where:
	  ◦ v = velocity (cm/sec)
	  ◦ Q = blood flow (mL/min)
	  ◦ A = cross-sectional area (cm2)
	• Blood velocity is higher in the aorta (small cross-sectional area) than in th Sum of all of the capillaries (large cross-sectional area).
	• The lower velocity of blood in the capillaries optimizes conditions for exchange of substances across the capillary wall

Capacitance (compliance)

- Describes the distensibility of blood vessels.
- Is inversely related to elastance, or stiffness. The greater the amount of elastic tissue there is in a blood vessel, the higher the elastance is, and the lower the compliance is.
- is expressed by the following equation
  - $C=V/P$
    - Where: C = capacitance or compliance (mL/mm Hg)
    - V = volume (mL)
    - P = pressure (mm Hg)

- Is directly proportional to volume and inversely proportional to pressure.
- Describes how volume changes in response to a change in pressure.
- Is much greater for veins than for arteries. As a result, more blood volume is contained in the veins (unstressed volume) than in the arteries (stressed volume).
- Changes in the capacitance of the veins produce changes in unstressed volume. For example, a decrease in venous capacitance decreases unstressed volume and increases stressed volume by shifting blood from the veins to the arteries.
- Capacitance of the arteries decreases with age; as a person ages, the arteries become stiffer and less distensible.

Pressure Profile in Blood Vessels

- As blood flows through the systemic circulation, pressure decreases progressively because of the resistance to blood flow.
- Thus, pressure is highest in the aorta and large arteries and lowest in the venae cavae.
- The largest decrease in pressure occurs across the arterioles because they are the site of highest resistance.
- Mean pressures in the systemic circulation are as follows:
  1. Aorta, 100 mm Hg
  2. Arterioles, 50 mm Hg
  3. Capillaries, 20 mm Hg
  4. Vena cava, 4 mm Hg

Venous Pressure

- Is very low.
- The veins have a high capacitance and, therefore, can hold large volumes of blood at low pressure

Atrial Pressure

- Left atrial pressure is estimated by the pulmonary wedge pressure.
- A catheter called Swan-Ganz catheter is used, inserted into the smallest branches of the pulmonary artery, makes almost direct contact with the pulmonary capillaries.
- Normally the measured pulmonary capillary pressure (PCWP) is approximately equal to the left atrial pressure.
- In Mitral Stenosis→PCWP > LV end diastolic pressure

Arterial Pressure

- Is pulsatile & is not constant during a cardiac cycle.

Systolic Pressure	• Is the highest arterial pressure during a cardiac cycle • Is measured after the heart contracts (systole) and blood is ejected into the arterial system.
Diastolic Pressure	• Is the lowest arterial pressure during a cardiac cycle • Is measured when the heart is relaxed (diastole) and blood is returned to the heart via the veins
Pulse Pressure	• **Is equal to = Systolic pressure – diastolic pressure** • Normal Pulse pressure= 40 mm Hg (120 – 80 = 40). • Pulse pressure is directly proportional to SV, • Inversely proportional to arterial compliance. • The most important determinant of pulse pressure is stroke volume. • Decreases in capacitance, such as those that occur with the aging process, cause increases in pulse pressure. • Examples:

Increase in Pulse Pressure	Decrease in Pulse Pressure
• Hyperthyroidism • Aortic regurgitation • Aortic stiffening (isolated systolic hypertension in elderly) • Obstructive sleep apnea (↑ sympathetic tone) • Exercise (transient)	• Aortic stenosis • Cardiogenic shock • Cardiac temponade. • Advanced heart failure (HF).

Mean Arterial Pressure

- MAP = **2/3rd diastolic pressure + 1/3rd systolic pressure**

OR

- MAP is also calculated as
  - = **Diastolic pressure + 1/3 of pulse pressure**
  - =80 + 40/3 = 93.3 mm Hg

OR

- Mean arterial pressure (MAP) = CO × total peripheral resistance (TPR)

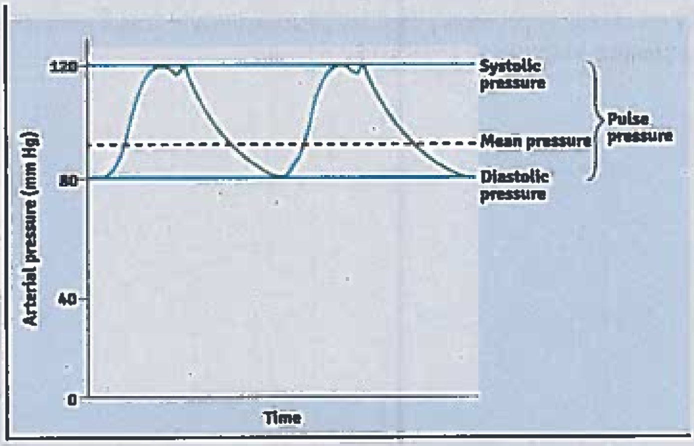


FIGURE 3.2 Arterial pressure during the cardiac cycle.

Cardiac Output and Its Variables

Cardiac Outputs	• CO = stroke volume (SV) × heart rate (HR)
	• in Exercise:
	  • During the early stages of exercise, CO is maintained by ↑HR and ↑SV.
	  • During the late stages of exercise, CO is maintained by ↑ HR only
	• Measurement of cardiac outputby the Fick principle
	  • Fick principle expressed as
	  • CO = (rate of O2 consumption
	  • The equation is solved as follows:
	  • O2 consumption for the whole body is measured.
	  • Pulmonary vein [O2] is measured in systemic arterial blood.
	  • Pulmonary artery [O2] is measured in systemic mixed venous blood.

Stroke Volume	• Is the volume ejected from the ventricle on each beat
	• is expressed by the following equation:
	  • Stroke volume = End-diastolic volume – End-systolic volume
	• ↑ SV with (mnemonic SV CAP)
	  • ↑ Contractility (e.g., anxiety, exercise)
	  • ↓ Afterload
	  • ↑ Preload (e.g., early pregnancy)

Preload	• Is end-diastolic volume (EDV), which is related to right atrial pressure • Depends on venous tone and circulating blood volume. • When venous return increases, end-diastolic volume increases and stretches or lengthens the ventricular muscle fibers (Frank-Starling relationship) • VEnous vasodilators (e.g., nitroglycerin) ↓prEload

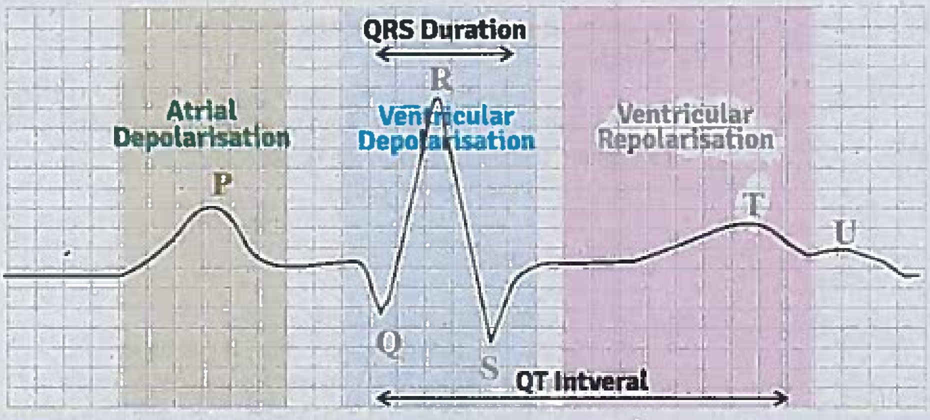
Afterload	• Afterload approximated by MAP.
	• ↑ Afterload ↑ pressure ↑wall tension per Laplace's law.
	• Chronic hypertension
	  • LV compensates for ↑ afterload by thickening (hypertrophy) in order to ↓ wall tension.
	• Drugs:
	  • Arterial vAsodilators (e.g., hydrALAzine)↓ Afterload (Arterial)
	  • ACE inhibitors and ARBs ↓ both preload and afterload.

Ejection Fraction	• $EF = \frac{SV}{EDV} = \frac{ESV-ESV}{EDV}$ • Is related to contractility. • EF ≥ 0.55 or 55%.

Contractility	• Contractility (and SV) ↑ with:
	  • Catecholamine stimulation via β1 receptor:
	  • ↑ intracellular Ca2+
	  • ↑ extracellular Na+ (↓activity of Na+/Ca2+ exchanger)
	  • Digitalis (blocks Na+/K+ pump) ↑intracellular Na+ ↓ Na+/Ca2+ exchanger activity ↑ intracellular Ca2+)

Myocardial O_2 Demand	• MyoCARDial O2 demand is ↑by:
	  • ↑Contractility
	  • ↑Afterload (proportional to arterial pressure)
	  • ↑Heart Rate
	  • ↑Diameter of Ventricle (↑ wall tension)

Electrocardiogram (ECG)



P wave	• Represents atrial depolarization
PR Interval	• Interval from the beginning of the P wave to the beginning of the Q wave (initial depolarization of the ventricle • Time from start of atrial depolarization to start of ventricular depolarization (normally <200 mSec). • Depends on conduction velocity through the atrioventricular (AV) node • Variations examples: ◦ Heart block→if AV nodal conduction decreases→the PR interval increases. ◦ stimulation of the sympathetic nervous system→increased conduction velocity through AV node→PR interval Is decreased ◦ stimulation of parasympathetic nervous system→decreased conduction velocity through AV node→PR interval is increased
QRS Complex	• Represents depolarization of the ventricles. • Atrial repolarization is masked by QRS complex
QT Interval	• Is the interval from the beginning of the Q wave to the end of the T wave • Represents the entire period of depolarization and repolarization of the ventricles.
ST Segment	• Is the segment from the end of the S wave to the beginning of the T wave • Is isoelectric. • Represents the period when the ventricles are depolarized
T Wave	• Represents ventricular repolarization • Tall t wave→Hyperkalemia, inverted T wave→hypokalaemia, MI and Ischemia
U wave	• Prominent in hypokalemia, bradycardia.
J wave	• Also, kown as Osborn wave, Seen in hypothermia

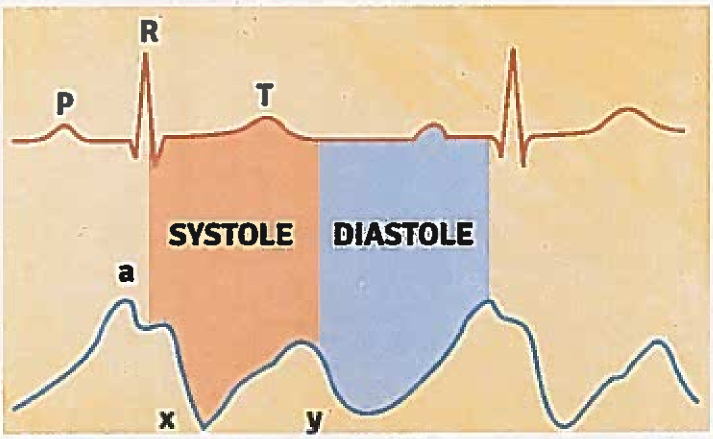
ECG Leads presentation

- Septal→V1, V2
- Anterior→V3, V4
- InFerior leads→Lead II, Lead III, and avF
- Lateral leads→Lead I , avL, V5 and V6

1 Lateral	aVR	V1 Septal	V4 Anterior
II Inferior	aVL Lateral	V2 Septal	V5 Lateral
III Inferior	aV Inefrior	V3 Anterior	V6 Lateral

Jugular Venous Curve

- a wave—atrial contraction. Absent in atrial fibrillation.
- c wave—RV ontraction (closed tricuspid valve bulging into atrium).
- x descent—atrial relaxation and downward displacement of closed tricuspid valve during ventricular contraction. Absent in tricuspid regurgitation.
- v wave—Inc. right atrial pressure due to filling ("villing") against closed tricuspid valve.
- y descent—RA emptying into RV.
- **Pathologies:**
    - a wave→Absent in atrial fibrillation, mitral stenosis
    - Giant "a" wave→Tricuspid Stenosis
    - Giant "v" wave→Tricuspid Regurgitation
    - x descent Absent in tricuspid regurgitation
    - y descent→Prominent in constrictive pericarditis, absent in cardiac tamponade.

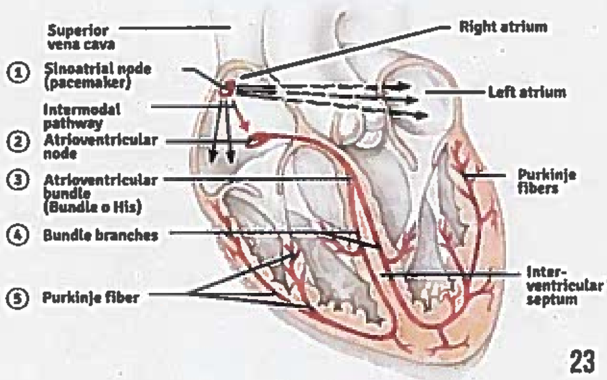


Conducting System of Heart

Conduction pathway	SA node→atria→AV node→bundle of His→right and left bundle branches→Purkinje fibers→ ventricles Left bundle branch divides into left anterior and posterior fascicles
Pacemaker rates	SA > AV > bundle of His/Purkinje/ventricles
Conduction Velocity	Purkinje > atria > ventricles > AV node

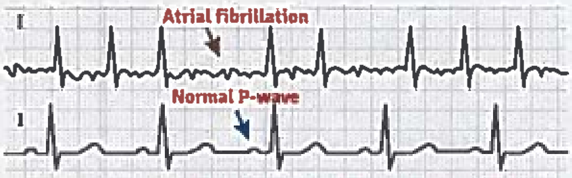
Location

- SA node =
    - Sub epicardium (upper portion of Crista terminalis)
- AV node =
    - Endocardium (located in posteroinferior part of interatrial septum
- Conducting system =
    - Subendocardium

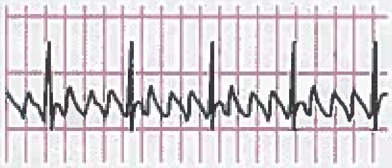


ECG Abnormalities

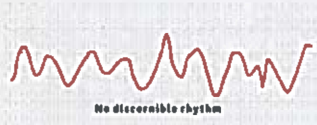
- **Atrial Fibrillation**
  - No discrete P waves in between irregularly spaced QRS complex
  - Irregular R-R interval



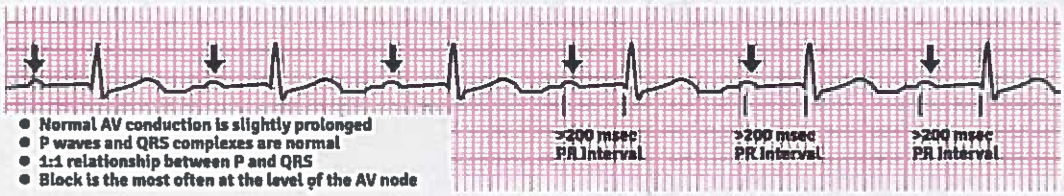
- **Atrial Flutter:**
  - Back to back atrial depolarization wave
  - Resulting in saw-tooth appearance
  - treatment: catheter ablation



- **Ventricular Fibrillation:**
  - Erratic rhythm with no identifiable waves
  - Fatal without immediate CPR and defibrillation



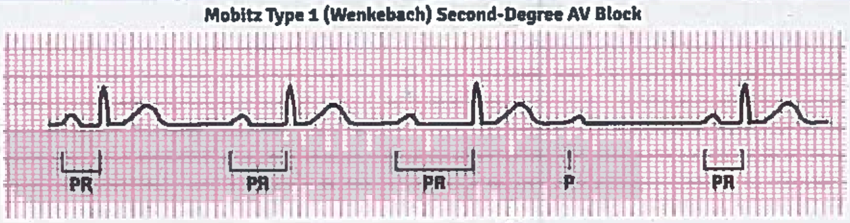
- **1st Degree Heart Block:**
  - The PR interval is prolonged (> 200 mSec).
  - No treatment required.



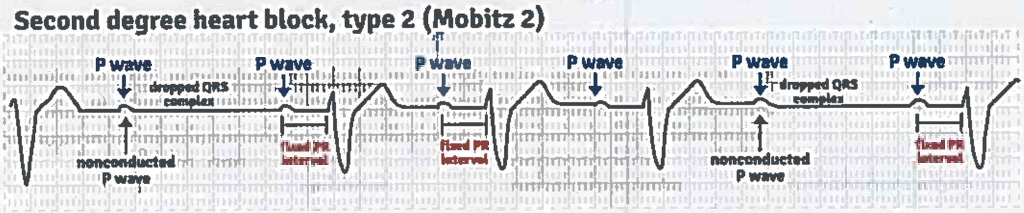
- **2nd Degree:**
  - In this condition dropped beats occur because some impulses from the atria fail to conduct to the ventricles.
  - It is of two types----Mobitz type-I and Mobitz type II

Type	Mobitz type- I (aka Wenckebach phenomenon)	Mobitz type- I (aka Wenckebach phenomenon)
Definition	• It is characterized by progressive lengthening of PR interval until a dropped beat occurs, and the cycle is repeated • Long PR interval until a beat is "dropped" (a P wave not followed by a QRS complex).	• It is characterized by a dropped beat without progressive lengthening of PR interval • May progress to 3rd-degree block. • Often treated with pacemaker.
Pathology	• Abnormality in AV node	• Abnormality in-HIS-Purkinje system

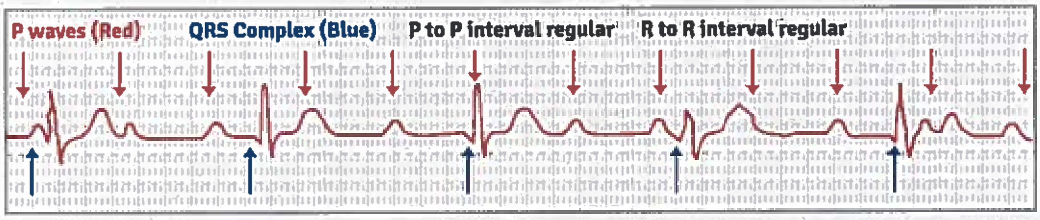
Mobitz Type 1 (Wenkebach) Second-Degree AV Block



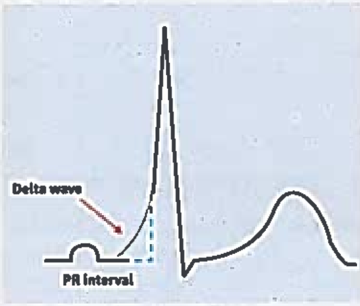
Second degree heart block, type 2 (Mobitz 2)



- **3rd Degree (Complete)**
  - It is characterized by no conduction through the atrioventricular node (AVN) so the atria and ventricles beat independently
  - Both P waves and QRS complexes are present
  - Although the P waves bear no relation to the QRS complexes.
  - Atrial rate is faster than ventricular rate.
  - Usually treated with pacemaker.
  - Lyme disease can result in 3rd-degree heart block.
  - **Canon A waves** (visible in neck due to large volume pulse from compensatory increase)



- **Wolff-Parkinson-White Syndrome**
  - Most common type of ventricular preexcitation syndrome.
  - Abnormal fast accessory conduction pathway from atria to ventricle bypasses the rate-slowing AV node
  - Characteristic delta wave with widened QRS complex and shortened PR interval on ECG
  - May result in re-entry circuit supraventricular tachycardia.



Heart Auscultation Area and Murmurs

Heart Auscultation Area (mnemonic APT M)	Murmurs	
• Aortic area→right 2nd intercostal space	• Aortic Stenosis	• Most common of all. • Crescendo decrescendo systolic ejection murmur. • Pulses are weak with delayed peak (pulsus parvus et tardus)
	• Aortic Regurgitation	• Blowing diastolic murmur. *Wide pulse pressure*
• Pulmonary area→left 2nd intercostal space	• Ventricular Septal Defect	• Harsh sounding murmur
	• Patent Ductus Arteriosus	• Continuous machinery like murmur, • Loudest at S2, often due to congenital rubella or prematurity
• Tricuspid area→left 4th intercostal space	• Tricuspid Regurgitation:	• High pitched blowing murmur. • Radiates to right sternal border, cause: RV dilation
• Mitral area→5th intercostal space (mid clavicular line--apex beat)	• Mitral Regurgitation:	• High pitched blowing pansystolic murmur. • Radiates towards axilla • Bifid p waves (due to left ventricular hypertrophy—also seen in mitral stenosis) cause: IHD, LV dilation.

Murmurs Made Easy

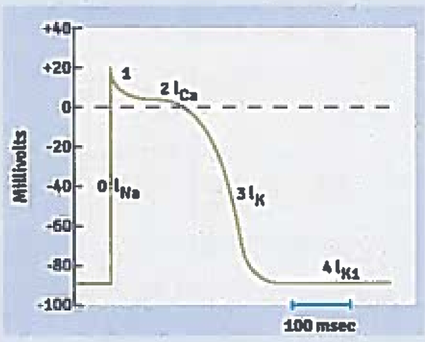
Systolic Murmurs	Diastolic Murmurs	Continuous Machine-Like Murmur
• Mitral regurgitation • Best heard at apex, radiates to axilla	• Mitral stenosis	• Patent ductus arteriosus
• Tricuspid regurgitation • Best heard at tricuspid area and radiates upward along sternal border	• Tricuspid stenosis	
• Aortic stenosis • Crescendo decrescendo systolic ejection murmur, radiates towards carotid	• Aortic regurgitation	
• Pulmonic stenosis • Best heard at pulmonic area	• Pulmonic regurgitation	
• Ventricular septal defect • Mitral valve prolapse		

- **Some key features of murmur**
  - **AR**-------------wide pulse pressure, early diastolic decrescendo murmur
  - **AS**------------ narrow pulse pressure, Crescendo-decrescendo ejection systolic murmur
  - **MS**------------ Mid-diastolic murmur---opening snap
  - **MR** ------------blowing pansystolic murmur at apex
  - **Mitral valve prolapse**------ mid-systolic click

Cardiac Action Potentials

- Inward current brings positive charge into the cell and depolarizes the membrane potential.
- Outward current takes positive charge out of the cell and hyperpolarizes the membrane potential

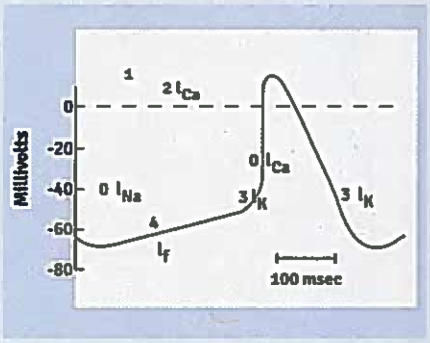
Ventricles, Atria, And The Purkinje System



- **Phase 0**
  - Rapid upstroke and depolarization
  - Voltage-gated Na+ channels open.
- **Phase 1**
  - initial repolarization
  - Inactivation of voltage-gated Na+ channels.
  - Voltage-gated K+ channels begin to open.
- **Phase 2**
  - Plateau of action potential
  - **Ca2+ influx through voltage-gated Ca2+ channels balances K+ efflux.**
  - Ca2+ influx triggers Ca2+ release from sarcoplasmic reticulum and myocyte contraction.
- **Phase 3**
  - Rapid repolarization
  - Massive K+ efflux due to opening of voltage-gated slow K+ channels
  - Closure of voltage-gated Ca2+ channels.
- **Phase 4**
  - Resting membrane potential
  - is a period during which inward and outward currents are equal and the membrane potential approaches the K+ equilibrium potential

Pacemaker Action Potential

- Occurs in the SA and AV nodes.
- Key differences from the ventricular action potential include:
- **Phase 0**
  - Upstroke
  - Opening of voltage-gated Ca2+ channels.
  - Fast voltage-gated Na+ channels are permanently inactivated because of the less negative resting potential of these cells.



- **Phase 1 and 2**
  - Are absent.
- **Phase 3**
  - Is Repolarization
  - Inactivation of the Ca2+ channels and ↑ activation of K+ channels→↑ K+ efflux.
- **Phase 4**
  - Is slow depolarization.
  - **Accounts for the pacemaker activity of the SA node (automaticity).**
  - Is caused by an **increase in Na+ conductance,** which results in an inward Na+ current called If.

Autonomic Effects on Heart Rate and Conduction Velocity

Chronotropic Action

- Chronotropic action is the frequency of heartbeat or heart rate.
- Through increasing or decreasing firing rate at SA node
- It is of two types:
  - Tachycardia or increase in heart rate
  - Bradycardia or decrease in heart rate.

Inotropic Action

- Force of contraction of heart is called inotropic action.
- It is of two types:
  - Positive inotropic action or increase in the force of contraction
  - Negative inotropic action or decrease in the force of contraction

Dromotropic Action

- Dromotropic action is the conduction of impulse through heart.
- By changing conduction velocity primarily in AV node.
- It is of two types:
  - Positive dromotropic action or increase in the velocity of conduction.
  - Negative dromotropic action or decrease in the velocity of conduction.

Parasympathetic Effects on Heart Rate And Conduction Velocity

- The SA node, atria, and AV node have parasympathetic vagal innervation, but the ventricles do not.
- The neurotransmitter is acetylcholine (ACh), which acts at muscarinic receptors.
- **Negative Chronotropic Effect:**
  - Decreases heart rate by decreasing the rate of phase 4 depolarization.
  - The mechanism of the negative chronotropic effect is decreased If, the inward Na+ current that is responsible for phase 4 depolarization in the SA node.
- **Negative Dromotropic Effect:**
  - Decreases conduction velocity through the AV node.
  - Increases the PR interval.
  - The mechanism of the negative dromotropic effect is decreased inward Ca2+ current and increased outward K+ current.

Sympathetic Effects On Heart Rate And Conduction Velocity

- Norepinephrine is the neurotransmitter, acting at β1 receptors.
- **Positive Chronotropic Effect:**

- Increases heart rate by increasing the rate of phase 4 depolarization.
- The mechanism of the positive chronotropic effect is increased If, the inward Na+ current that is responsible for phase 4 depolarization in the SA node.

- **Positive Dromotropic Effect:**
  - Increases conduction velocity through the AV node.
  - Action potentials are conducted more rapidly from the atria to the ventricles, and ventricular filling may be compromised.
  - Decreases the PR interval.
  - The mechanism of the positive dromotropic effect is increased inward Ca2+ current

Cardiac Muscle Contraction

Steps in Excitation–Contraction Coupling

- The action potential spreads from the cell membrane into the T tubules.
- During the plateau of the action potential, Ca2+ conductance is increased and Ca2+ enters the cell from the extracellular fluid (inward Ca2+ current) through L-type Ca2+ channels (dihydropyridine receptors).
- This Ca2+ entry triggers the release of even more Ca2+ from the SR (Ca2+-induced Ca2+ release) through Ca2+ release channels (ryanodine receptors).
- Intracellular [Ca2+] increasesCa2+ binds to troponin C, and tropomyosin is moved out of the way, removing the inhibition of actin and myosin bindingmyocardial cell contracts.
- Relaxation occurs when Ca2+ is re-accumulated by the SR by an active Ca2+-ATPase pump.

Frank-Starling Relationship

- States that the greater the venous return, the greater the cardiac output and stroke volume.

Inotropism (Contractibility)

Factors That Increase Contractility (Positive Inotropism)

- Increased Heart Rate
  - When more action potentials occur per unit time, more Ca2+ enters the myocardial cells during the action potential plateaus, more Ca2+ is stored in the SR, more Ca2+ is released from the SR, and greater tension is produced during contraction.
  - Examples of the effect of increased heart rate are
    - Positive staircase phenomenon or Bowditch staircase (or Treppe).
    - When a quiescent heart is stimulated after prolong rest, first few contractions gradually increase in size and then becomes steady
- Sympathetic stimulation (catecholamines) via β1 receptors
  - increases the force of contraction by two mechanisms:
  - It increases the activity of the Ca2+ pump of the SRas a result, more Ca2+ is accumulated by the SR and thus more Ca2+ is available for release in subsequent beats.
- Cardiac Glycosides (Digitalis)
  - Increase the force of contraction by inhibiting Na+-K+-ATPase in the myocardial cell membrane (shown in fig)

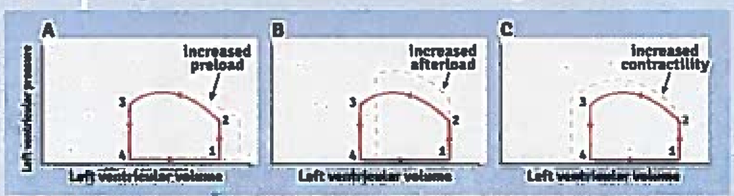
	• As a result of this inhibition, the intracellular [Na+] increases, diminishing the Na+ gradient across the cell membrane. • Na+-Ca2+ exchange (a mechanism that extrudes Ca2+ from the cell) depends on the size of the Na+ gradient and thus is diminished, producing an increase in intracellular [Ca2+].
Factors That Decrease Contractility (Negative Inotropism)	• Parasympathetic stimulation (ACh) via muscarinic receptors decreases the force of contraction in the atria by decreasing the inward Ca2+ current during the plateau of the cardiac action potential

Ventricular Pressure–Volume Loops

- Are constructed by combining systolic and diastolic pressure
- A single left ventricular cycle of contraction, ejection, relaxation, and refilling can be visualized by combining the two curves into a pressure–volume loop.
- **Step 1: 1→2 (isovolumetric contraction)**
  - Begins at end of diastole, and blood present in ventricles is EDV.
  - Blood from atria enters ventricles
  - As a result, ventricular pressure increases
  - When ventricular pressure increases more than atria pressure mitral valve closes
  - Because all valves are closed, no blood can be ejected from the ventricle (isovolumetric)
- **Step 2: 2→3 (ventricular ejection).**
  - Ventricle pressure exceeds pressure in the aorta.
  - The aortic valve opens and blood is ejected into the aorta (stroke volume).
- **Step 3: 3→4 (isovolumetric relaxation)**
  - The ventricle has done its work, now relaxes.
  - When ventricular pressure decreases to less than aortic pressure, the aortic valve closes.
  - Because all of the valves are closed again, ventricular volume is constant (isovolumetric)
- **Step 4: 4→1 (ventricular filling).**
  - Left ventricular pressure keeps on decreasing, till less than left atrial pressure
  - The mitral valve opens and filling of the ventricle begins.
  - During this phase, ventricular volume increases to about 140 mL (EDV).

Changes in the Ventricular Pressure–Volume Loop

Increased Preload	• Refers to an increase in end-diastolic volume and is the result of increased venous return • According to Frank-Starling →↑venous return→↑stroke volume→↑width of the pressure-volume loop.
Increased Afterload	• Refers to an increase in aortic pressure. • The ventricle must eject blood against a higher pressure, resulting in a decrease in stroke volume. • ↓stroke volume→↓ width of the pressure–volume loop. • ↓stroke volume→↑end-systolic volume.
Increased Contractility	• Ventricle contraction ↑→↑stroke volume. • ↑stroke volume→↓end-systolic volume



URE 3.10 Effects of changes in (A) preload, (B) afterload, and (C) contractility on the ventricular pressure-volume low

Cardiac Cycle

- Opening and closing of valves causes the physiologic heart sounds.
- When all valves are closed, ventricular volume is constant, and the phase is called isovolumetric

Atrial systole	• On ECG→is preceded by the P wave • On venous curve →presented by "a" wave • In ventricular hypertrophy, filling of the ventricle by atrial systole causes the 4th heart sound, which is not audible in normal adults.
Isovolumetric ventricular contraction	• Period between mitral valve closing and aortic valve opening; period of highest O2 consumption • Begins during the QRS complex, which represents electrical activation of the ventricles. • When ventricular pressure becomes greater than atrial pressure, the AV valves close produces→1st heart sound. • Because the mitral valve closes before the tricuspid valve, the first heart sound may be split. • Ventricular pressure increases isovolumetrically, however no blood leaves the ventricle during this phase because the aortic valve is closed.
Rapid ventricular ejection	• When ventricular pressure ↑ more than aortic pressure, the aortic valve opens. • Ventricular volume decreases dramatically because most of the stroke volume is ejected during this phase. • Atrial filling begins.
Reduced ventricular ejection	• Ejection of blood from the ventricle continues, but is slower. • Ventricular pressure begins to decrease. • Aortic pressure also decreases because of the runoff of blood from large arteries into smaller arteries. • Atrial filling continues.
Isovolumetric ventricular relaxation	• Repolarization of the ventricles is now complete (end of the T wave). • The aortic valve closes, followed by closure of the pulmonic valve. • Closure of the semilunar valves corresponds to the→2nd heart sound. • Inspiration delays closure of the pulmonic valve and thus causes splitting of the second heart sound. • Ventricular pressure decreases rapidly because the ventricle is now relaxed. • Ventricular volume is constant (isovolumetric) because all of the valves are closed.
Rapid ventricular filling	• When ventricular pressure becomes less than atrial pressure, the mitral valve opens. • With the mitral valve open, ventricular filling from the atrium begins. • Aortic pressure continues to decrease because blood continues to run off into the smaller arteries. • Rapid flow of blood from the atria into the ventricles causes the → 3rd heart sound, • 3rd heart sound → normal in children but, in adults, is associated with disease.

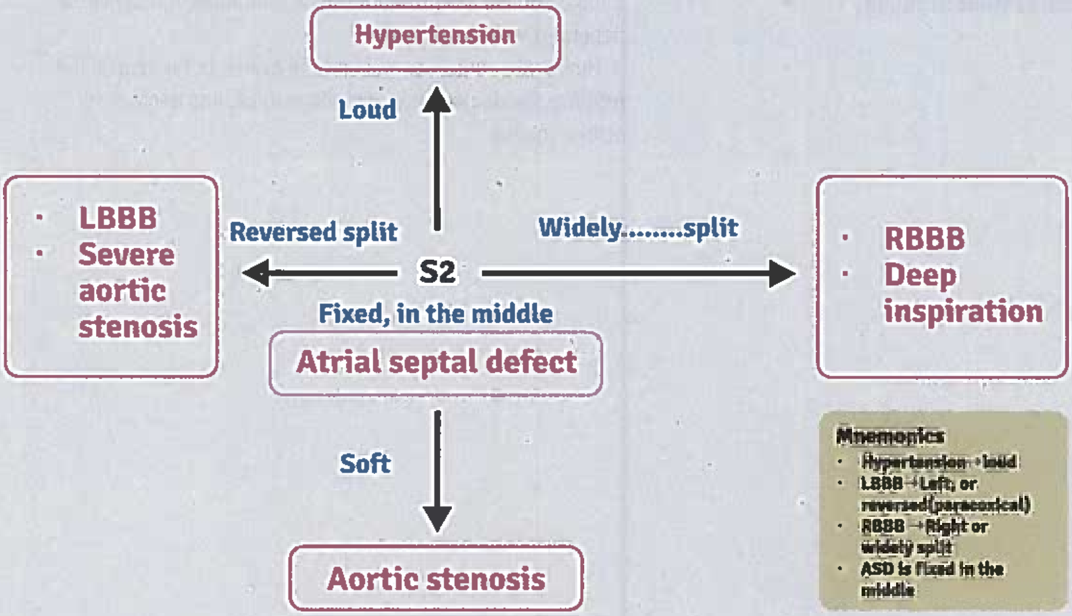
Reduced ventricular filling	•	Longest phase → Ventricular filling continues, but slower → depends on HR
	•	↑ Heart rate cause decreased time available for ventricular refilling, decreased end-diastolic volume, and decreased stroke volume.

Heart Sounds

Heart Sound	Reason	Notes
S1	Isovolumic contraction, mitral and tricuspid valve closure	**S1 is longer than S2** While Low frequency, low intensity compared to S2
S2	Isovolumic relaxation, aortic and pulmonary valve closure	Inspiration delays closure of the pulmonic valve and thus causes splitting of the second heart sound.
S3	Also known as **Gallop rhythm or ventricular gallop** due to rapid ventricular filling phase	**(e.g., mitral regurgitation, HF)** Normal in children but, in adults, is associated with disease.
S4	In late diastole ("atrial kick"). Also called **atrial gallop**	Associated with ventricular hypertrophy **(HOCM)**

Splitting of heart sounds

Type	Causes
Loud S2	• HTN
Soft S2	• Aortic stenosis
Reversed or paradoxical split S2 • When the pulmonic valve closes before the Aortic valve,	• (left) LBBB, severe aortic stenosis
Widely split S2 • When it takes longer to the pulmonic valve to close.	• RBBB, deep inspiration
Fixed in the middle • When splitting doesn't change with inspiration	• Atrial septal defect



Mnemonics
- Hypertension→loud
- LBBB→Left, or reversed(paradoxical)
- RBBB→Right or widely split
- ASD is fixed in the middle

Regulation of Arterial Pressure

Baroreceptor Reflex

Location	• Carotid sinus • Aortic arch
Negative Feedback System	• Fast, neural mechanisms and responsible for the minute-to-minute regulation of arterial blood pressure
Aortic Arch	• **Respond to increases, but not to decreases, in arterial pressure** • The aortic arch baroreceptors are innervated by the aortic nerve, which then combines with the vagus nerve (cranial nerve X)
Carotid Sinus	• **Responds to both, increase as well as to decrease in arterial pressure** • Located at bifurcation of common carotid arteries • The carotid sinus baroreceptors are innervated by the sinus nerve of Hering, which is a branch of the glossopharyngeal nerve (IX)
Steps in Baroreceptor Reflex	• ↓In arterial pressure → ↓ stretch on the walls of the carotid sinus. → • ↓Stretch → ↓ the firing rate of the carotid sinus nerve [Hering's nerve, which is a branch of the glossopharyngeal nerve (IX)] → which carries information to the vasomotor center in the brain stem. • MAP (set point is 100mm hg) less than 100 mm Hg, baroreceptor carries messages to vasomotor center → which increases blood pressure toward normal by the following mechanism 1. ↓ Parasympathetic outflow 2. Sympathetic outflow • ↑HR, ↑contractility, ↑stroke volume, ↑CO • ↑ constriction of veins → ↑venous return → ↑CO • ↑ constriction of arteries → ↑ TPR → ↑arterial pressure

Renin-Angiotensin-Aldosterone System

- Slow, hormonal mechanism, for long term BP control
- ↓ arterial pressure → ↓ renal perfusion → Renin release from juxtaglomerular cells of the afferent arteriole
- Renin causes conversion of angiotensin to angiotensin-I
- Angiotensin-I is converted to angiotensin II, by ACE primarily in lungs
- Effect of angiotensin II
    - ↑ synthesis and secretion of aldosterone, which causes increases Na+ reabsorption by the renal distal tubule, thereby increasing extracellular fluid (ECF) volume, blood volume, and arterial pressure
    - It increases thirst and therefore water intake.
    - It causes vasoconstriction of the arterioles, thereby increasing TPR and arterial pressure

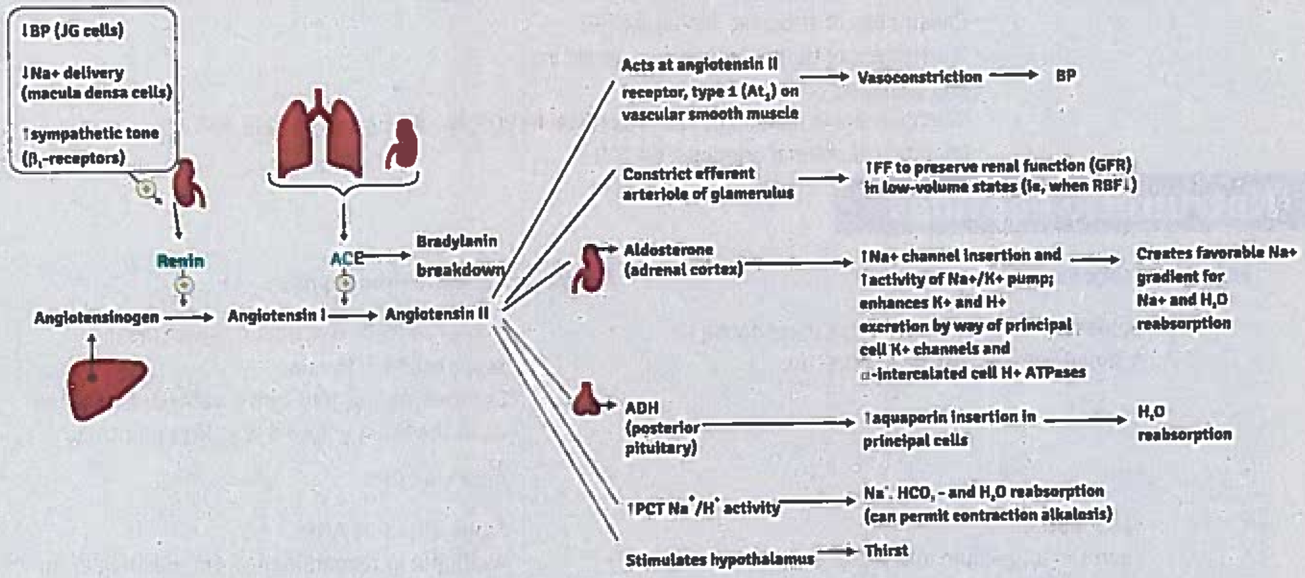
Cerebral ischemia

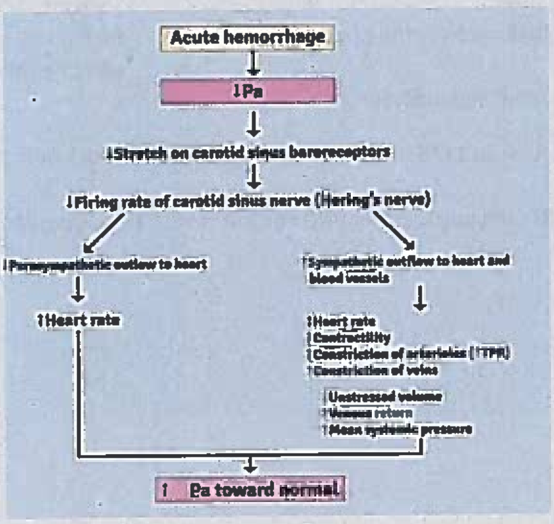
- When brain ischemic → PCO_2 ↑ in brain → chemoreceptors in vasomotor area ↑ sympathetic activity
- Constriction of arterioles → peripheral vasoconstriction and ↑ TPR → blood flow to other organs (e.g. kidneys) is ↓ so as to preserve blood flow to brain
- Example (Cushing reaction)
    - ↑ ICP Cerebral ischemia and ↑PCO2 in brain → ↑sympathetic activity ↑ arterial pressure

Note: Cushing Reflex:

- **Triad of Bradycardia. Hypertension, Respiratory depression**

Renin-angiotensin-aldosterone system





Autoregulation

- It shows how blood flow to an organ remains constant over a wide range of perfusion pressures.

Organ	Factors Determining Autoregulation
Heart (coronary circulation)	• The most important local metabolic factors are hypoxia (↓O2) and adenosine
Brain	• The most important local metabolic factors → CO2 (pH)
Kidneys	• Myogenic (muscle contracts when stretched), and tubuloglomerular
Lungs	• Hypoxia causes vasoconstriction (only in lungs hypoxia causes vasoconstriction otherwise it causes everywhere vasodilation)
Skeletal muscle (CHALK)	• Local metabolites during exercise: CO2, H+, Adenosine, Lactate, K+, • At rest: sympathetic tone
Skin	• Sympathetic stimulation most important mechanism for temperature control

Example of Effect of Exercise on Cardiovascular System

- Exercise: ↑ blood flow will occur with
  - Central command (↑sympathetic outflow, ↓parasympathetic)
    - ↑HR, ↑Contractility→↑stroke volume, ↑cardiac output
    - Constriction of arterioles increases TPR
    - Constriction of veins increases venous return
  - Local response:
    - Dilatation due to metabolites such as **(CHALK)** CO2, H+, Adenosine, Lactate, K+
    - Dilatation of skeletal arterioles→↓TPR

Natriuretic Peptides

Atrial Natriuretic Peptide	B-Type (Brain) Natriuretic Peptide
• Released from atrial myocytes in response to ↑ blood volume and atrial pressure	• Released from ventricular myocytes in response to ↑ tension • Synthesized largely by the ventricles (as well as in the brain where it was first identified).
• Acts via cGMP	• Acts via cGMP
• Vasodilation	• Same effect as ANP
• Excretion of sodium and water by augmenting glomerular filtration rate	• Available in recombinant form (nesiritide) for treatment of HF.
• Inhibiting sodium reabsorption in the proximal tubule, and	• BNP blood test used for diagnosing HF (very good negative predictive value).
• Inhibiting release of renin and aldosterone	

- Circulating levels of ANP and BNP are elevated in congestive heart failure but not sufficient to prevent edema formation
- Concentrations of ANP and particularly BNP correlate with a poor prognosis in heart failure

Chapter 3:
Respiratory System

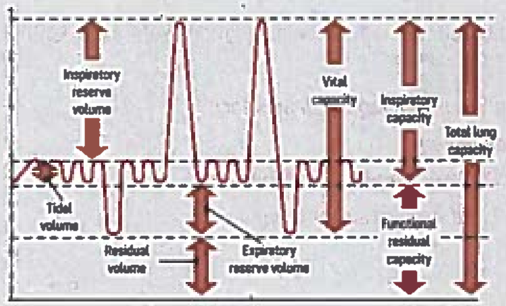
Lung Volumes

Tidal volume (V_T, TV)	• **Is the volume inspired or expired with each normal breath.** • 0.5L (or 500mL)
Inspiratory reserve volume (IRV)	• **Is the volume that can be inspired over and above the tidal volume** • Is used during exercise. • 2-3 L
Expiratory reserve volume (ERV)	• **vIs the volume that can be expired after the expiration of a tidal volume** • 1.2 L
	• **vIs the volume that remains in the lungs after a maximal expiration** • vCannot be measured by spirometry. • vIncreases with age • 1.2 L

Lung Capacities

(Note: a capacity is a sum of ≥ 2 physiologic volumes)

Inspiratory capacity	• Is the sum of tidal volume and IRV
Functional residual capacity (FRC)	• **Is the sum of ERV and RV** Is the volume remaining in the lungs after a tidal volume is expired Includes the RV, so it cannot be measured by spirometry.
Vital capacity (VC), or forced vital capacity (FVC)	• **Is the sum of tidal volume, IRV, and ERV** Is the volume of air that can be forcibly expired after a maximal inspiration Decreases with age
Total lung capacity (TLC)	• **Is the sum of all four lung volumes** Is the volume in the lungs after a maximal inspiration includes RV, so it cannot be measured by spirometry



RV	FRC – ERV
Vital capacity	IRV + TV + ERV
Inspiratory capacity	IRV + TV
Functional residual capacity	ERV + RV
Total lung capacity	IRV + TV + ERV + RV

- ***NOTE***: *Most volumes & capacities can be measured by using a spirometer, but residual volume and any capacity containing the residual volume cannot be measured with a spirometer. TLC, FRC & RV cannot be measured using simple spirometry.*

FEV_1 TO FVC (Forced vital capacity) ratio

- Forced expiratory volume (FEV1) measures air movement in and out of lungs
- Forced expiratory volume at 1 second is FEV1
- *It is expressed as FEV1/FVC = 0.7 (or 70%)*

Obstructive Vs. Restricitve Lung Diseases

	Obstructive lung diseases	Restrictive lung diseases
Total lung capacity	↑	↓
Residual volume (RV)	↑	↓
FEV1	↓↓↓	Normal or ↓
FEV1/FVC	Decreased (Less than 0.7 or 70%)	Increased (more than 0.7 or 70%)
Examples	Bronchial asthma COPD Bronchiectasis Cystic Fibrosis	Farmer's lung (hypersensitivity pneumonitis) Ankylosing spondylitis Sarcoidosis Silicosis TB Bronchiolitis obliterans Drugs (hydralazine, INH, Amiodarone) Rheumatologic disease (SLE, RA, Scleroderma)

Dead space

- Volume of air which is inhaled that does not take part in the gas exchange.

Anatomical Dead Space	Physiological Dead Space
• Volume of air which is inhaled but that does not take part in the gas exchange because it remains in the conducting airways (from nose to terminal bronchiole).	• Physiological dead space includes anatomical dead space plus air in alveoli that are not perfused or poorly perfused
• Approximately equal to 150mL	• Is approximately equal to the anatomic dead space in normal lungs. • May be greater than the anatomic dead space in lung diseases in which there are Ventilation /perfusion (V/Q) defects.
	• is calculated by the following equation (Bohr equation): • $V_D = V_T \times \frac{PACO2 - PECO2}{PACO2}$ *Where V_D= physiological dead space* *V_T= tidal volume* *P_{ACO2}= PCO2 of arterial blood (mm Hg)* *P_{ECO2}=P_{CO2} of expired air (mm Hg)*

Factors Affecting Dead space

- Pattern of breathing has no effect on dead space but if asked, dead space does not change in answer is shallow breathing

Increased Dead space	Decreased Dead space
• Emphysema	• *Atelectasis*
• Neck Extension	• Neck Flexion
• Bronchoconstriction	• Bronchodilation
• ETT intubation	• *Tracheostomy*
• Standing	• Sleep
• Smoking	• Hyperventilation
• *Hypotension*	• Supine Position
• Diseases such as Pneumonia, ARDS, Bronchitis, Asthma, Cardiac Failure, Pulmonary Embolism	

Ventilation

Minute ventilation	Alveolar ventilation
• It is the total volume of gas entering in lungs per minute	• *It is the total volume of air entering the alveoli per minute*
• Minute ventilation = V_T × RR/min • Normally RR/min average= 12/min • Tidal volume= 500mL	• *$V_A = (V_T - V_D)$ × RR/min.* • *Where V_D = dead space (150mL)* • *V_T= tidal volume (500 mL)* • *Normally RR/min average= 12/min*

- Example: (taken from past paper)
  - Question: Calculate Alveolar ventilation where Tidal volume is 500ml/respiration, with normal dead space. RR is 10/min
  - Alveolar ventilation = (500 – 150) × 10= 3500mL/min answer

Mechanism Of Respiration

Inspiration	Expiration

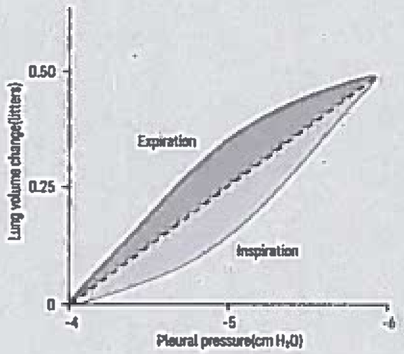
• Inspiration is active process	• Expiration is normally passive, because of elasticity returns to its resting position
	• Expiratory muscles are used during
	  • Exercise
	  • ↑ Airway resistance disease
	  • e.g., COPD or asthma

• **Diaphragm (C3 to C5)**
  • Diaphragm is the primary muscle of inspiration.
  • When the diaphragm contracts in inspiration, initially the lower ribs are fixed and the dome of the diaphragm descends, *thus increasing the vertical diameter of thorax.*
	• **Abdominal muscles**
	  • Compress the abdominal cavity, push the diaphragm up, and push air out of the lungs.

• **External intercostal and accessory muscles**
  • Are not used for inspiration during normal quiet breathing.
  • Are used during exercise and in respiratory distress
  • Accessory muscles involved in forced inspiration are Pectoralis major and minor, Serratus anterior, Scalene group of muscles and sternocleidomastoid
  • The direction of the muscle fibers is downward and forwards, as they contract, they push the sternum forward (pump-handle movement) increasing the ***antero-posterior diameter of thorax***. At the same time the ribs also move outwards like the handle of bucket (bucket-handle movement) increasing the ***transverse diameter of thorax***
	• **Internal intercostal muscles**
	  • Pull the ribs downward and inward.

Compliance of lung

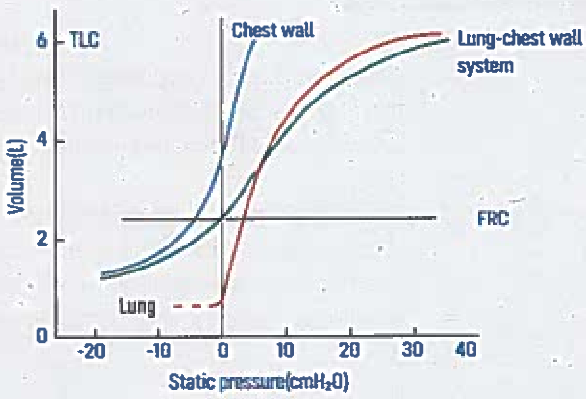
- Defined as change in volume per unit change in the pressure.
- Expressed as
  - $C = \Delta V / \Delta P$
  - (Where C=compliance, V= volume, P=pressure)
- Inversely proportional to wall stiffness.
- High Compliance (Compliance=lungs Cooperate) = lung easier to fill



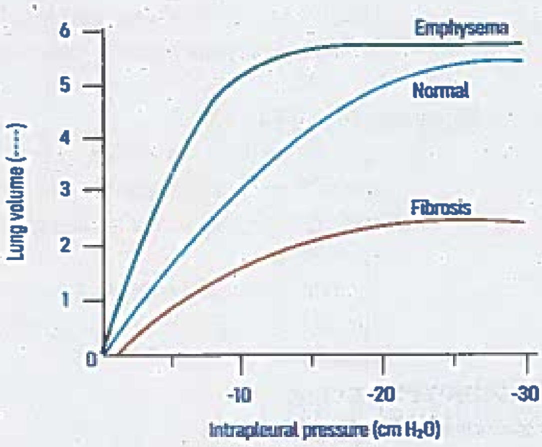
- Compliance increases due to loss of elastic property of lung tissues, which occurs both in physiological and pathological conditions:
    - Physiological condition: old age
    - Pathological condition: Emphysema
- Lower compliance = lung harder to fill (pulmonary fibrosis, pneumonia, NRDS, pulmonary edema).
- **Hysteresis**—lung inflation curve follows a different curve than the lung deflation curve due to need to overcome surface tension forces in inflation, as shown in fig

Compliance of lung-chest wall system

- **At the resting (muscles relaxed) volume (FRC):**
    - The tendency of the isolated lungs is to collapse and the tendency of the isolated chest wall is to expand
    - Both forces being equal and opposite, therefore, the combined lung-chest wall system neither collapse nor expand (i.e., equilibrium/ at zero shown in fig.)
    - Because of two opposing forces, intrapleural pressure is negative (i.e., subatmospheric, *value -5 cm of H_2O*)



- **Changes in lung compliance:**
    - **Pneumothorax:**
        - Air introduced into intrapleural space, intrapleural pressure becomes equal to atmospheric (normally negative intrapleural pressure/subatmospheric), lungs collapse (natural tendency) and chest wall spring outward (natural tendency)
    - **Emphysema:** Lung compliance ↑→ higher FRC*chest becomes barrel shaped*
    - **Fibrosis:** Lung compliance →↓ lower FRC



Surfactant and Surface Tension

- **Surfactant:**
    - ***Synthesized by type-II alveolar cells, and consists primarily of dipalmitoylphosphotidylcholine (DPPC).***
    - Lines the alveoli, and keep alveoli dry.
    - ***↓surface tension and ↑ lung compliance (easier to fill).***
    - *In the fetus, Surfactant may be present as early as gestational week 24 and is almost always present by gestational week 35.*
    - *Generally, a lecithin: sphingomyelin ratio greater than 2:1 in amniotic fluid reflects mature levels of surfactant.*
    - Neonatal respiratory distress syndrome →↓ surfactant →↓ compliance difficult to inflate lungs→↓ Ventilation/perfusion defect → *ground glass appearance of lung fields*

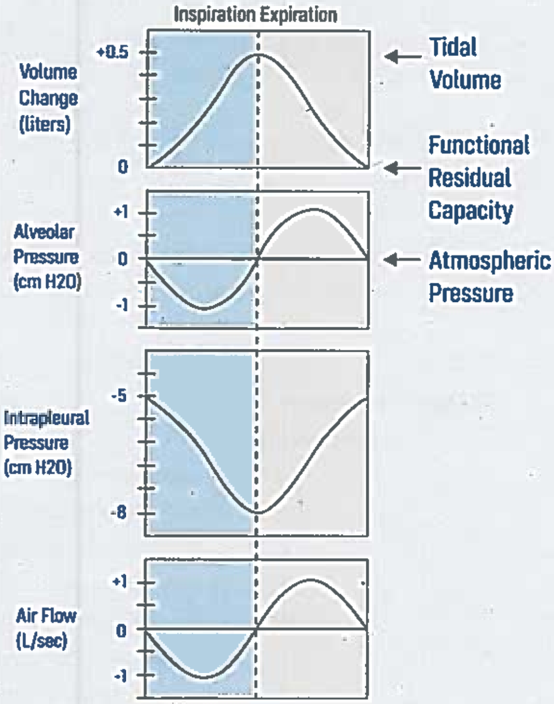
- **Surface tension:**
    - Represented by Laplace's law which is
        - **P=2T/r** (where P=collapsing pressure, r=radius, T =surface tension)
    - It means that radius is inversely proportional to collapsing pressure, means small alveoli smaller radius high collapsing pressure and vice versa.

Sympathetic and parasympathetic effect on lungs

- *Parasympathetic stimulation → constrict airways, ↓radius → ↓ resistance.*
- *Sympathetic stimulation dilate airways,→ ↑ radius, ↓resistance*

Breathing cycle

- **At rest (FRC)**
    - Already explained in compliance of lung above that at rest no air moves in and out of lungs so lung volume= FRC, alveolar pressure is equal to zero
    - Natural phenomenon lungs try to collapse and chest wall spring outwards as a result of two opposing forces generate negative pressure intrapleural pressure is negative i.e. -5cm of H_2O



- **During inspiration (FRC + V_t)**
    - Lung volume↑ → as a result pressure in alveoli → ↓ from zero to negative. The pressure inside is less than that of outside so air moves into lungs.
    - Lung volume ↑ → elastic recoil also↑→ so intrapleural pressure becomes more negative.

- **During expiration (FRC – V_t)**
    - Lung volume↓ → as a result pressure in alveoli ↑ → becomes positive. The pressure inside is more than that of outside so air moves out of lungs.
    - Lung volume↓ → elastic recoil also↓→ intrapleural pressure returns to its resting value.

Diffusion of gases

- Lung diffusion capacity (D_L) increases during exercise, because more open capillaries → so more surface area for diffusion
- Lung diffusion capacity (DL) decreases in
    - Emphysema → Decreased surface area
    - Fibrosis and pulmonary edema → Increased in diffusion distance.
- ***Lung diffusion capacity (D_L) is measured with carbon monoxide (D_{LCO})***

Perfusion limited exchange

- ***Illustrated by N_2O and CO_2 and O_2 under normal conditions.***
- Gas equilibratespartial pressure between alveolar air and arterial blood equals so no exchange occurs which is limited due to perfusion
- So, diffusion of the gas can occur only with ↑ in blood flow---that's why called perfusion limited exchange

Diffusion limited exchange

- ***Illustrated by CO, O_2 (during strenuous exercise, emphysema, fibrosis)***

increase distance for diffusion and in emphysema due to decrease surface area → partial pressure does not equal, so diffusion continues. And thus, exchange of gases is limited due to diffusion.

Hemoglobin

- Hemoglobin (Hb) is composed of 4 polypeptide subunits (as in adults=2 α and 2 β)
- Adult Hb=$\alpha 2\beta 2$ while Fetal Hb → $\alpha 2\gamma 2$ (β-chains are replaced by γ-chains).
- The iron in hameoglobin is normally in a reduced state I.e., is in the ferrous state (Fe^{2+}), which binds O_2.
  - Mnemonic: (Ferro**us** Fe^{2+}; "just the **2** of **us**").
- Hb increases the O_2-carrying capacity of blood 70 times

Oxygen content

- *Normally 1g Hb can bind 1.34 mL O_2 Normal Hb amount in blood is 15 g/dL.*
- **O_2 content = (Hb conc × O_2-binding capacity × SaO_2) + (0.003 × PaO_2)**
  - Hb = hemoglobin concentration; SaO_2 = arterial O_2 saturation
  - PaO_2 = partial pressure of O_2 in arterial blood, O_2 binding capacity = 20 mL O_2/dL of blood
- *With ↓ Hb there is ↓O_2 content of arterial blood, but no change in O_2 saturation and Pao_2*
- **Conditions**

	Hb concentration	% O_2 SAT Of Hb	Dissolved O_2 (PaO_2)	Total O_2 Content
CO Poisoning	Normal	↓ (CO competes with O2)	Normal	↓
Anemia	↓	Normal	Normal	↓
Polycythemia	↑	Normal	Normal	↑

Methemoglobin

- Iron in Hb is normally in a reduced state (ferro**us** Fe**2**+; "just the **2** of **us**").
- Oxidized form of Hb (ferric, Fe3+) does not bind O2 as readily as Fe2+, leading to tissue hypoxia from ↓ O2 saturation and ↓ O2 content.
- Methemoglobinemia
  - Refers to hypoxemia *after exposure to an oxidizing agent ((eg, local anesthetics,*
  - dapsone, nitrites) that oxidizes ferrous iron (Fe2+) to ferric iron (Fe3+), resulting in impaired oxygen transportation
  - Methemoglobinemia may present with cyanosis and *chocolate-colored blood.*
  - Treatment: Methylene blue.

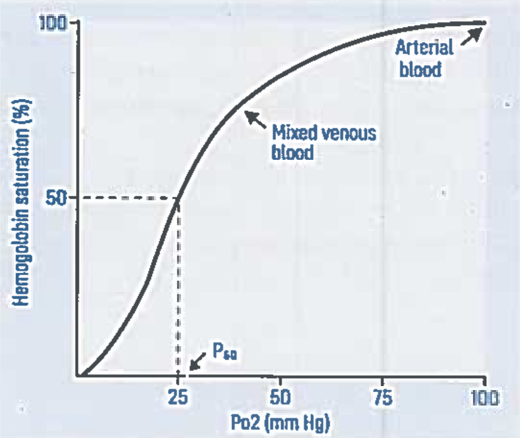
Cyanide vs Carbon Monoxide Poisoning

	Cyanide	Carbon monoxide
Introduction	• Both inhibit aerobic metabolism via inhibition of complex IV (cytochrome c oxidase) hypoxia; that does not fully correct with supplemental O2 and ↑ anaerobic metabolism. • Both can lead to *pink or cherry red skin* (usually postmortem finding), seizures, and coma	
• **Source**	• Byproduct of synthetic product combustion, ingestion of amygdalin (cyanogenic glucoside found in apricot seeds) or cyanide	• Odorless gas from fires, car exhaust, or gas heaters

	Cyanide	Carbon monoxide
• Signs/Symptoms	• Breath has bitter almond odor; • Cardiovascular collapse.	• Headache, dizziness. • Multiple individuals may be involved (eg, family with similar symptoms in winter). • Classically associated with bilateral globus pallidus lesions +on MRI, although rarely seen with cyanide toxicity as well
• Treatment	• Hydroxocobalamin (binds cyanide→ cyanocobalamin→ renal excretion). • Nitrites (oxidize Hb → methemoglobin → binds cyanide→ cyanomethemoglobin→ less toxicity). • Sodium thiosulfate (↑ cyanide conversion to thiocyanate → renal excretion).	• *100% O2, hyperbaric O2.*
• Effect On Oxygen-Hemoglobin Dissociation Curve	• Curve normal; • Oxygen saturation may appear normal initially.	• *Left shift in curve* → ↑ affinity for O2→↓ O2 unloading in tissues. Binds competitively to Hb with 200× greater affinity than O2 to form carboxyhemoglobin→ ↑ *%O2 saturation of Hb.*

Hb-O_2 dissociation curve

- When each successive O2 molecule binds to a heme site result in a change in the affinity of hemoglobin (called positive cooperativity), resulting in sigmoid shape of the curve
- Binding of the first O_2 molecule increases the affinity for the second O_2 molecule, and so forth. Thus, the affinity for the fourth O_2 molecule is the highest.
- This change in affinity facilitates the loading of O_2 in the lungs (flat portion of the curve) and the unloading of O_2 at the tissues (steep portion of the curve).



Hb-O_2 dissociation curve changes

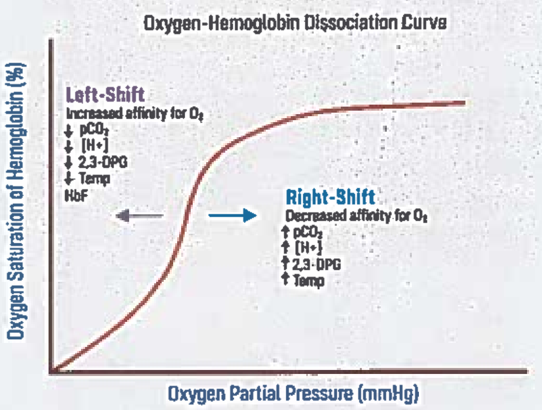
- The oxygen dissociation curve describes the relationship between the percentage of saturated hemoglobin and partial pressure of oxygen in the blood.
- It is not affected by hemoglobin concentration.

Shifts to Left = Lower oxygen delivery (High O_2 affinity so less delivery to tissues)	Shifts to Right = Raised oxygen delivery (Low O_2 affinity so raised O_2 delivery to tissues)
• *Low H+*	• Raised H+
• *Low PCO_2 (or increased pH/↓acidity)*	• Raised PCO_2 (or ↓in pH/↑ acidity)—Bohr effect)
• *Low 2,3-DPG*	• Raised 2,3-DPG
• *Low temperature*	• Raised temperature
• *HbF*	
• *CO poisoning*	

Note: (About 2,3 DPG)

It is present in RBC's; it enhances the ability of RBCs to release oxygen near tissues that need it most.
It interacts with β-chains of Hb→↓affinity for O_2 and promotes the release of O_2
As fetal Hb has no β-chains so→↓ affinity for O_2 → thus O_2 affinity for fetus is higher than that of adult this →results in movement of O_2 from mother to fetus

• ***Explanation:*** 1. *HbF:* · *αα2γ2 (β-chains are replaced by γ-chains) due to which↑affinity for oxygen, so lower oxygen delivery* 2. *CO poisoning* *The affinity of hemoglobin for CO is 200 times its affinity for O_2.* *When CO binds with Hb; the affinity (craving) of remaining sites ↑ for O_2, causing a shift of the curve to the left.*	• ***Explanation:*** 1. *During exercise (increase in temperature), the tissues produce more CO_2, which decreases tissue pH and, through the Bohr Effect, stimulates O_2 delivery to the exercising muscle*



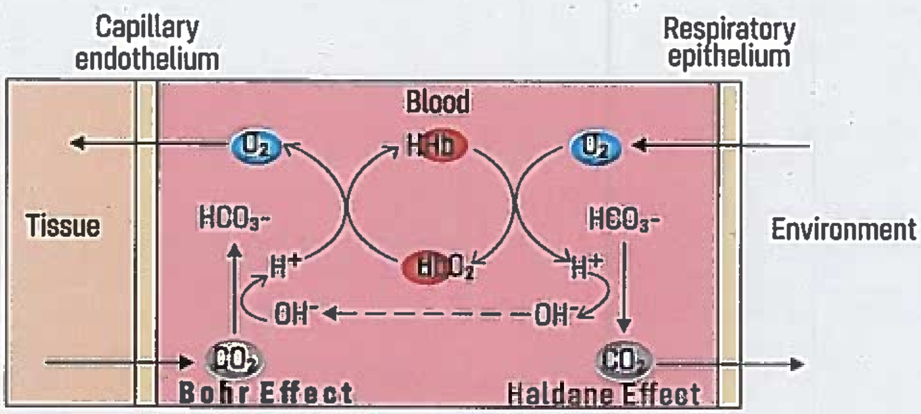
Oxygen-Hb Dissociation Curve

CO_2 transport

- CO_2 is transported from tissues to lungs in three forms:
  Dissolved CO_2 (5-9%).
  Carbaminohemoglobin (21-25%), which is CO2 bound to hemoglobin ($HbCO_2$)
  HCO_3 (from hydration of CO_2 in the RBCs), which is the major form (90%)

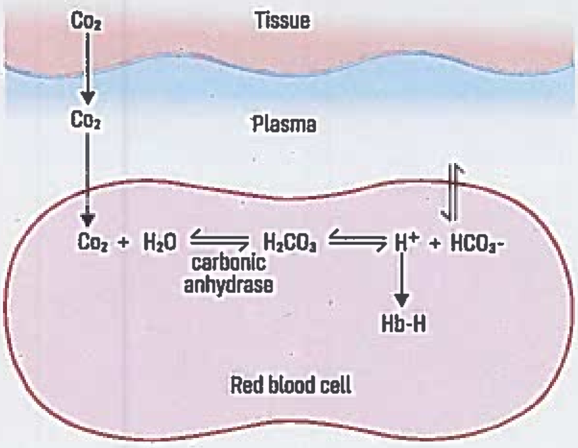
Bohr vs. Haldane effect

Bohr Effect	Haldane effect:
• Oxygen-hemoglobin dissociation curve is inversely related both to acidity and to the concentration of carbon dioxide ◦ O2 - HB curve a $\frac{1}{\text{acidity-Co2}}$ • This means that raised PCO_2 (or↓in pH/↑acidity) ↓Hb-O2 affinity→ *shifts curve to <u>R</u>ight, unloading O2 (Boh<u>R</u> effect).so↑delivery of O2 to tissues.*	• The Haldane Effect describes the phenomenon by which binding of oxygen to hemoglobin promotes the release of carbon dioxide. • So, Increase PO_2 means CO_2 binds less well to Hb. • Mnemonic: *HaLdane effect= Left shift, bohR effect= Right shift*



Chloride Shift

- It is defined as HCO_3 leaves the RBCs in exchange for Cl-.
- <u>Occurs as follow in RBC's</u>
  - CO_2 combines with H_2O to form H2CO3, catalysed by carbonic anhydrase.
  - H_2CO_3 dissociates into H+ and HCO_3o
  - HCO_3 leaves the RBCs in exchange for Cl- (chloride shift) and is transported to the lungs in the plasma
- <u>In lungs reverse chloride shift occurs</u>
  - HCO_3 enters the RBCs in exchange for Cl-.
  - HCO_3 recombines with H+ to form H_2CO_3.
  - H_2CO_3 decomposes into CO_2 and H_2O.
  - Thus, CO_2, originally generated in the tissues, is expired.



Hypoxemia (↓ PaO_2)

Hypoxia and hypoxemia and effect on Erythropoietin

- *Hypoxemia is a decrease in arterial Po_2*
- *A-a gradient is used to measure causes of hypoxemia*

- A-a gradient = $P_{AO2} - P_{aO2}$
  - Where P_{AO2} = alveolar PO_2
  - And P_{aO2} = arterial O_2

	Normal A-a gradient	↑A-a gradient
Value	• 0-10mm Hg	• >10mm Hg
Definition	• O_2 equilibrates between alveolar gas and arterial blood	• O_2 does not equilibrate between alveolar gas and arterial blood
Causes	• High altitude • Hypoventilation • In both above causes there is ↓ alveolar and as well as ↓arterial O_2. So, both equilibrates and results in normal A-a gradient	• Diffusion defect (e.g., fibrosis) V/Q defect Right to left shunt • In all the above causes the alveolar O_2 is normal but there is decreased arterial O_2. So A-a gradient is ↑.

Hypoxia

- Hypoxia is decreased O_2 delivery to the tissues.
  - O_2 delivery = Cardiac output × O_2 content of blood
- **Types of Hypoxia:**

Type	Definition	Example
Hypoxemic Hypoxia	The oxygen pressure is low	*High altitude, abnormal ventilation perfusion*
Anemic Hypoxia	Amount of Hb to carry oxygen is low	*Blood loss, anemia, CO poisoning*
Stagnant Hypoxia	Blood flow to the tissue is low	*Heart failure, shock*
Histotoxic Hypoxia	Tissue can't utilize O_2	*Cyanide poisoning*

Erythropoietin (EPO)

- *Growth factor that is synthesized in the kidneys in response to hypoxia*
  - ***Hypoxia → ↑ EPO synthesis → ↑erythrocytes → ↑O_2 delivery.***

Respiratory System Response to Exercise

Exercising muscle → ↑ CO_2 production and ↑ O_2 consumption. → ↑Ventilation rate to match O_2 consumption and CO_2 production.
In exercise → ↑ cardiac output as a result ↑ pulmonary blood flow → ↑ V/Q(ventilation/perfusion) becomes more uniform from apex to lungs

- Note: no change in mean value for arterial PO_2 and PCO_2. But ↑ in venous CO_2

Respiratory System Response To High

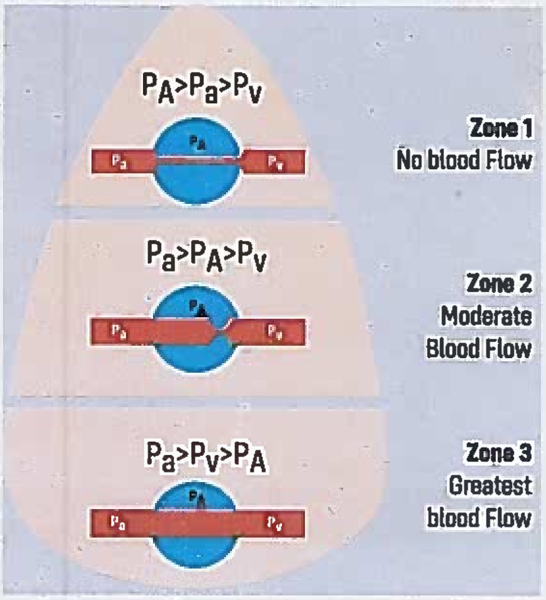
- At high altitude→↑ atmospheric oxygen →↑ Alveolar O_2 as well as Arterial O_2 (hypoxemia)
- Hypoxemia→stimulates peripheral chemoreceptors→↑ventilation which causes respiratory alkalosis→ called altitude sickness. (Can be treated with acetazolamide)
- Hypoxemia →also stimulates erythropoietin production →↑RBC'S→↑02 content of blood.
- Hypoxemia →↑ 2, 3 DPG synthesis →↑ 02 delivery to tissues. (Hb-O_2 curve right shift)

Pulmonary blood flow

- In supine position blood flow is uniform throughout the lungs
- In standing position due to effect of gravity *blood flow lowest at apex and highest at base.*
- **Zones of lung**

Zone 1 (Area of NO/low blood flow)	• Alveolar pressure (P_A) > arterial pressure Pa> venous pressure P_v i.e. • (P_A>Pa>Pv) • high alveolar pressure may compress the capillaries reducing blood flow
Zone-2 (Area of moderate blood flow)	• Because of gravity arterial pressure increases more than alveolar pressure i.e. • (Pa>P_A>Pv)
Zone-3 (Area of greatest blood flow)	• Here because of gravity, arterial and venous pressure is greater than alveolar pressure. i.e. • Pa>PV>P_A

Note: **Pulmonary blood flow is measured by applying Fick principle.**



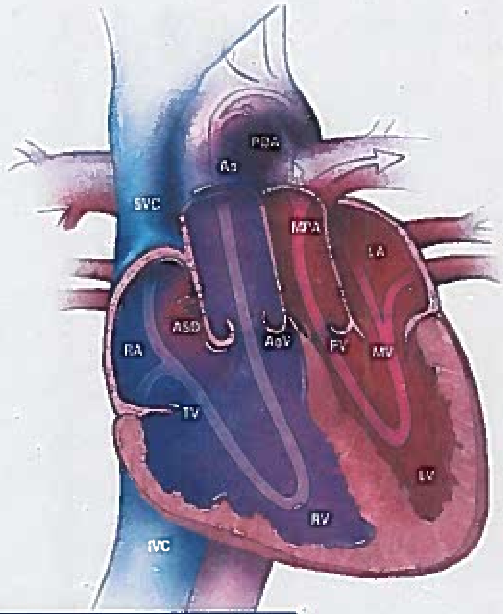
Pulmonary Blood Flow Response to Hypoxia

- *In all organs, hypoxia causes vasodilation but it is opposite in lungs, where it causes vasoconstriction*

Shunts

	Right-To-Left Shunts	Left-To-Right Shunts
Example	• Tetralogy of Fallot	• Congenital abnormalities (e.g., patent ductus arteriosus) or traumatic injury
Arterial PO2	• Decrease in arterial PO_2 because of the admixture of venous blood with arterial blood	• Do not result in a decrease in arterial PO2. • Instead, PO_2 will be elevated on the right side of the heart because there has been admixture of arterial blood with venous blood

Trancus arteriosus

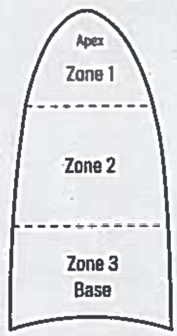


Ventilation and perfusion defects (V/Q)

- It is ratio of alveolar ventilation (V) to pulmonary blood flow (Q).
- **Normal value = 0.8**

V/Q in different parts of lung

Zone- 1 (apex) Zone- 1 (apex)	Ventilation is low, and Blood flow is very low	$\frac{\downarrow V}{\downarrow\downarrow Q} = \uparrow V/Q$ As a result, PO_2 is high and PCO_2 is low at apex
Zone-3 (base)	Ventilation is higher, and blood flow is much higher	$\frac{\uparrow V}{\uparrow\uparrow Q} = \downarrow V/Q$ As a result, PO_2 is low and PCO_2 is high at base



Q	V	V/Q	Po2	Pco_2
↓↓	↓	↑	↑	↓
↑↑	↑	↓	↓	↑

Note: certain organism (e.g., Mycobacterium tuberculosis) that grows best at high O_2 will affect apex of lungs, because apex of lungs has high PO_2.

V/Q in Airway Obstruction

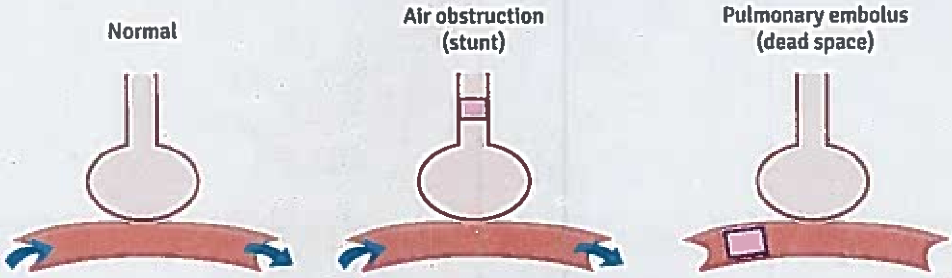
If airway blocked, ventilation is zero and if blood flow normal then $\frac{V}{Q} = \frac{Zero}{Q}$ =ZERO, called shunt

- *So there is no gas exchange, PO_2 and PCO_2 of pulmonary capillary blood will approach their values in mixed venous blood*
- *So there is no gas exchange, PO_2 and PCO_2 of pulmonary capillary blood will approach their values in mixed venous blood*

V/Q in Pulmonary Embolism

- *If blood flow is completely blocked (e.g. by an embolism occluding pulmonary artery), then blood flow is zero, if ventilation normal then $\frac{V}{Q} = \frac{Normal}{Zero}$ **=infinity**, which is called dead space (anything divided by zero is infinity)*
- *So there is no gas exchange, PO_2 and PCO_2 of alveolar air will approach their values in inspired air*

V/Q DEFECTS



V/Q	0.8	0	∞
P_{AO_2}	100 mm Hg	--	150 mm Hg
P_{ACO_2}	40 mm Hg	--	0 mm Hg
P_{aO_2}	100 mm Hg	40 mm Hg	--
P_{aCO_2}	40 mm Hg	46 mm Hg	--

Control Of Breathing

Central Control of Breathing

Cerebral Cortex

- Breathing can be under voluntary control, can hold breath or can take rapid breath and can result in hypoventilate or hyperventilate

Medullary Respiratory Center

- Located in Reticular Formation

Dorsal Respiratory Group	Ventral Respiratory Group
• *Responsible for inspiration*	• *Responsible for expiration*
• *Input comes from vagus and glossopharyngeal nerve*	• *Not active during normal breathing*
• *Output travels via phrenic nerve to diaphragm*	• *Active when expiration is active e.g. Exercise*

Apneustic Center And Pneumotaxic Center

Apneustic Center	Pneumotaxic Center
• Apneustic CIs located in the lower pons.enter	• Is located in the upper pons.
• Stimulates inspiration	• Inhibits inspiration
• Producing a deep and prolonged inspiratory gasp (apneusis)	• Therefore, regulates inspiratory volume and respiratory rate

Chemoreceptors for CO_2, H+ and O_2

Central Chemoreceptors	Location	• ***Present in Medulla***
	Pathogenesis	• ***Sensitive to the pH of the cerebrospinal fluid (CSF).*** *↓CSF pH →↑ breathing rate (hyperventilation).*
	Mechanism	• ↑CO_2 →CO_2 + H_2O → H_2CO_3 → H+ + HCO3 • CO2 diffuses from arterial blood into the CSF • In the CSF, CO2 combines with H2O to produce H+ and HCO3 • The resulting H+ acts directly on the central chemoreceptors. • Thus, increases in Pco2 and [H+] stimulate breathing, and decreases in Pco2 and [H+] inhibit breathing. • The resulting hyperventilation or hypoventilation then returns the arterial Pco2 toward normal.
Peripheral Chemoreceptors	Location	• *In the carotid and aortic bodies* • The carotid bodies are located at the bifurcation of the common carotid arteries. • The aortic bodies are located above and below the aortic arch.
	Pathogenesis And Mechanism	• *↓ Po2 (if <60 mm Hg)→↑breathing rate* • *↑Pco2 →↑breathing rate* • *↓pH (acidosis) →↑ breathing rate→ by stimulating carotid body*

Other Types of Receptors for Control of Breathing

Lung stretch receptors (Hering-Breuer reflex)	• *Located in the smooth muscle of the airways, 'when stimulated by distention of the lungs, they produce a reflex decrease in breathing frequency*
Irritant receptors	• Located between the airway epithelial cells, stimulated by noxious substances (e.g., dust and pollen).
J (juxtacapillary) receptors	• Located in the alveolar walls, close to the capillaries. • Engorgement of the pulmonary capillaries, as in LHF, stimulates it causing rapid, shallow breathing

Chapter 4: Renal

CELL

- Cell is defined as structural and functional unit of body.
  The entire body, contains about 100 trillion cells.
  The red blood cells, numbering 25 trillion most abundant and others 75 trillion additional cells of other typesthat perform functions different from those of the red cell

Difference between ECF and ICF

TBW = Antipyrene, D_2O, Titrated H_2O.

Extracellular fluid (Inulin, mannitol)	Intracellular Fluid (TBW − ECF)

• *1/3rd of total body water.*
• Present in spaces outside the cell
• Contains nutrients and ions essential for cell life that is why also called as internal environment of body
• *Major cations (positive charged ions): **Na+***
• *Major anions (negative charged ions): **Cl^-** and **HCO_3^-***
• Further divided into
  ◦ ***Plasma:*** RISA, Evans blue
    ▪ *1/4th of ECF*
    ▪ *Part of ECF present in blood*
    ▪ *contains plasma proteins*
  ◦ ***Interstitial fluid:*** (ECF − plasma vol.)
    ▪ *3/4th of ECF*
    ▪ *Part of ECF present in space between cells.*
    ▪ *contains little protein as compared to plasma→ultra-filtrate of plasma*
	• 2/3rd of total body water
	• It contains large amounts of potassium, magnesium, and phosphate ions.
	• *Major cations: **k+ and Mg+***
	• *Major anions: **proteins.***
	  ◦ Mnemonic: **HIKIN** (**HI**gh **K** **IN**side)

- **60-40-20 rule**
  - TBW is **60%** of body weight, ICF is **40%** of body weight., ECF is **20%** of body weight
    - *So------Total body water in litres in a 70kg person is → 70 × 0.6 = 42 L*
    - *---------ICF in litres in a 70kg person is → 70 × 0.4 = 28 L*
    - *---------ECF in litres in a 70kg person is → 70 × 0.2 = 14 L*

Measuring the Volumes of the Fluid

Compartment	Marker Used to Measure Volume	Major Cations	Major Anions
TBW	Tritiated H_2O *D_2O* Antipyrene		
ECF	Sulfate *Inulin* *Mannitol*	Na+	Cl- HCO3
Plasma (1/4 of ECF)	RISA (radioiodinated serum albumin) *Evans blue*	Na+	Cl- HCO3- Plasma protein
Interstitial (3/4 of ECF)	ECF minus plasma volume	Na+	Cl- HCO3-
ICF	TBW minus ECF	K+	Organic phosphates Protein

Shifts of Water between Compartments

Some Basics

- Osmosis is the flow of water from low solute to high solute concentration solution
- Osmolarity is concentration of solute particles.
- Plasma osmolarity (P_{osm}) is estimated as:
  - $P_{osm} = 2 \times Na^+ + \frac{Glucose}{18} + \frac{Bun}{2.8}$
- At steady state, ECF osmolarity and ICF osmolarity are equal.
- To achieve this equality, water shifts between the ECF and ICF compartments.
- It is assumed that solutes such as NaCl and Mannitol do not cross cell membranes and are confined to ECF

Example of Shift of Fluid between Compartments

Fluid Type	ECF Volume	Osmolarity of ECF	Shift Of Water And Results On ICF And ECF	Plasma Protein Concentration And Hematocrit
Infusion of isotonic NaCl/ Isotonic fluid	↑	No change--as the fluid is isotonic	As no change in osmolarity, no shift of water b/w ICF and ECF	• <u>ECF volume ↑</u> ◦ So, it dilutes protein→↓ plasma protein ◦ it dilutes RBC→↓ hematocrit
Diarrhea (loss of isotonic fluid)	↓	No change--as the fluid is isotonic	As no change in osmolarity, no shift of water b/w ICF and ECF	• <u>ECF volume ↓</u> ◦ So, it concentrates protein →↓ plasma protein ◦ it concentrates RBC→↓ hematocrit

Fluid type	ECF vol.	ECF osm.	Shifts of water & And results on ICF & ECF	Plasma protein conc. & Hematocrit
Excessive NaCl intake		↑ ECF osmolarity -- because osmoles has been added	Water shifts from ICF to ECF (because water molecules move from low solute to high solute concentration) as a result ↑ECF,ICF↓	• ECF↑ • So, it dilutes protein ↓ plasma protein • It dilutes RBC ↓ hematocrit
Sweating in desert (Remember in sweating— more water is lost than salt)	↓	↑ --because more water is lost than salt, so osmoles concentration is high comparatively	Water shifts out of cell ICF to ECF (because water molecules move from low solute to high solute concentration) as a result, ↑ECF, ↓ICF	• <u>ECF volume</u> ↓ • ↑ plasma protein • **<u>But hematocrit unchanged</u>** • Because water shifts out of the RBCs, decreasing their volume and offsetting the concentrating effect of the decreased ECF volume
SIADH – gain of water	↑ (because of water retention	↓	Water shifts inside cell from ECF to ICF	• <u>ECF volume</u> ↑ • ↓ Plasma protein concentration • **<u>But hematocrit unchanged</u>** • Because water shifts into RBCs, increasing their volume and offsetting the diluting effect of the gain of ECF volume

Renal Clearance

- Indicates the volume of plasma cleared of a substance per unit time. The units of clearance are mL/min or mL/24 hour.
  - $C = \frac{UV}{P}$ (mnemonic: **UV** light shining on **P**ee)

    where:
    - C = clearance (mL/min or mL/24 hour)
    - U = urine concentration (mg/mL)
    - V = urine volume/time (mL/min)
    - P = plasma concentration (mg/mL)

Renal Blood Flow

↓RBF	Sympathetic nervous system and angiotensin II→ causing vasoconstriction
↑RBF	Prostaglandins E2 and I2, bradykinin, nitric oxide, and dopamine→causing vasodilation

Autoregulation of RBF

- RBF remains constant from 80 to 200 mm Hg by changing renal vascular resistance
  Mechanisms:
  - Myogenic mechanism
    - ↑renal arterial pressure→↑stretch→ renal afferent arterioles contract in response to stretch increasing resistance to maintain constant blood flow
  - Tubuloglomerular feedback
    - ↑renal arterial pressure→↑fluid to macula densa which causes constriction of afferent arterioles increasing resistance to maintain constant blood flow

Measurement of Renal Plasma Flow (RPF)

- *Renal plasma flow (RPF) can be estimated using para-aminohippuric acid (PAH) clearance.*
- Between filtration and secretion, there is nearly 100% excretion of all PAH that enters the kidney
  - $RPF = C_{PAH} = U_{PAH} \times V / P_{PAH}$
    - Where as,
      - RPF = renal plasma flow (mL/min or mL/24 hour)
      - C_{PAH} = clearance of PAH (mL/min or mL/24 hour)
      - $[U]_{PAH}$ = urine concentration of PAH (mg/mL)
      - V = urine flow rate (mL/min or mL/24 hour)
      - $[P]_{PAH}$ = plasma concentration of PAH (mg/mL)

Glomerular Filtration Rate

- Inulin clearance can be used to calculate GFR
- Because it is freely filtered and is neither reabsorbed nor secreted
  - $GFR = C_{inulin} = U_{inulin} \times V / P_{inulin}$
    - where:
      - GFR = glomerular filtration rate (mL/min or mL/24 hour)
      - [U]inulin = urine concentration of inulin (mg/mL)
      - V = urine flow rate (mL/min or mL/24 hour)
      - [P]inulin = plasma concentration of inulin (mg/mL)

Determination of GFR

- **GFR decreases Both BUN and serum creatinine increase**
- GFR decreases with age, although serum creatinine remains constant because of decreased muscle mass

Starling Forces

- GFR can be expressed by the Starling equation as
  - $GFR = K_f[(P_{GC} - P_{BS})] - (\pi_{GC} - \pi_{BS})]$

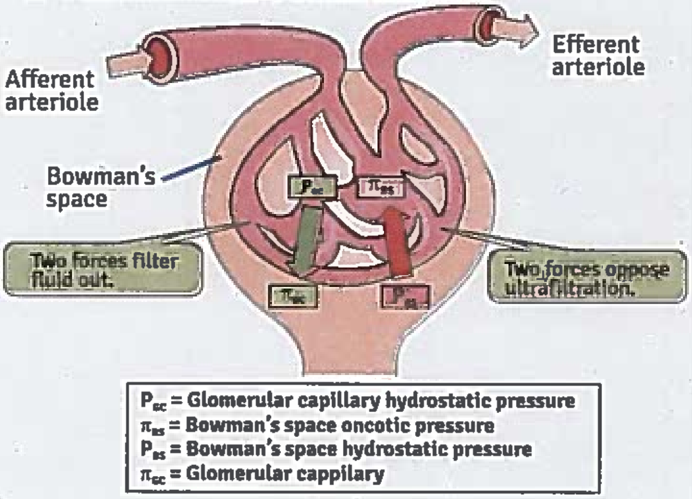
Where

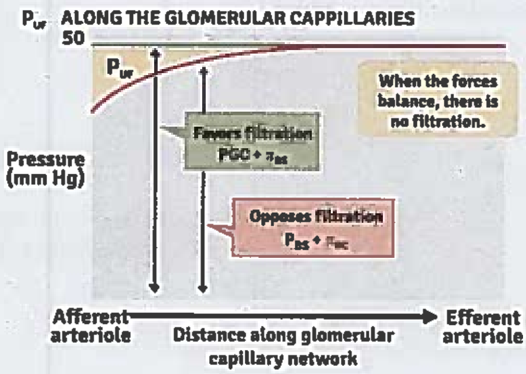
GFR is filtration across the glomerular capillaries	***Normal GFR = 100 mL/min.***
Kf is the filtration coefficient of the glomerular capillaries	Normally, negative charges line the glomerular capillaries→restrict filtration of plasma proteins, which are also negatively charged
P_{GC} is glomerular capillary hydrostatic pressure	*↑by dilation of the afferent arteriole or constriction of the efferent arteriole (e.g., angiotensin II)* *↑ in P_{GC} cause ↑ net ultrafiltration pressure and GFR*
P_{BS} is Bowman space hydrostatic pressure	*↑ by constriction of the ureters* *↑ in P_{BS} cause→ ↓ in net ultrafiltration pressure and GFR*

• π_{GC} is glomerular capillary oncotic pressure	• Increased by increases in protein concentration • ↑ in π_{GC} cause decreases in net ultrafiltration pressure and GFR. • Normally increases along the length of the glomerular capillary because filtration of water increases the protein concentration of glomerular capillary blood.
• π_{BS} is Bowman space oncotic pressure	• It is usually zero, and therefore ignored, because only a small amount of protein is normally filtered

- In short
  - ↑ P_{GC} (Capillary hydrostatic pressure) → ↑ GFR
  - ↑ P_{BS} (Bowman space hydrostatic pressure) → ↓ GFR
  - ↑ π_{GC} (Capillary oncotic pressure) → ↓ GFR
  - Afferent arteriole constriction → ↓ GFR
  - Efferent arteriole constriction → ↑ GFR
  - ↑ Plasma protein concentration → ↓ GFR
  - ↓ Plasma protein concentration → ↑ GFR

A FORCES AFFECTING ULTRAFILTRATION





Changes in Glomerular Dynamics

	GFR	RPF	Filtration Fraction (GFR/RPF)
• *Afferent Arteriole Constriction*	↓	↓	—
• *Efferent Arteriole Constriction*	↑	↓	↑
• ↑ Plasma Protein Concentration	↓	—	↓
• ↓ Plasma Protein Concentration	↑	—	↑
• Constriction of ureter	↓	—	↓
• Dehydration	↓	↓↓↓	↑

Calculation of Reabsorption and Secretion

- Filtered load = GFR X PLASMA
- Excretion rate= V X urine
- Reabsorption rate = Filtered load -Excretion rate
- Secretion rate = Excretion rate - Filtered load

- Filtered load > excretion rate= net reabsorption of the substance occurred
- Filtered load < excretion rate= net secretion of the substance occurred

Reabsorption and Secretion of Different

Glucose — Reabsorption of glucose by Na^+-glucose cotransport in the PCT

- *Plasma glucose concentrations < 200 mg/dL→ all of the filtered glucose can be reabsorbed*
- *Plasma glucose concentrations > 375 mg/dL, the carriers are saturated called Tm (transport maximum)→ so no reabsorption*

Excretion of glucose

- Plasma glucose concentrations < 200 mg/dL → all of the filtered glucose can be reabsorbed, so excretion is zero

  Plasma glucose concentrations > 375 mg/dL, the carriers are saturated called Tm→ so no→ reabsorption so if the plasma concentration increases, the additional filtered glucose cannot be reabsorbed and is excreted in the urine

Threshold

- *Defined as the plasma concentration at which glucose first appears in the urine is approximately 200 mg/dl*

Splay

- Splay is the region of substance clearance between threshold and Tm due to the heterogeneity of nephrons

NOTE:

- *Normal pregnancy may decrease ability of PCT to reabsorb glucose and amino acids→ glucosuria and aminoaciduria.*

Clearances Of Substances

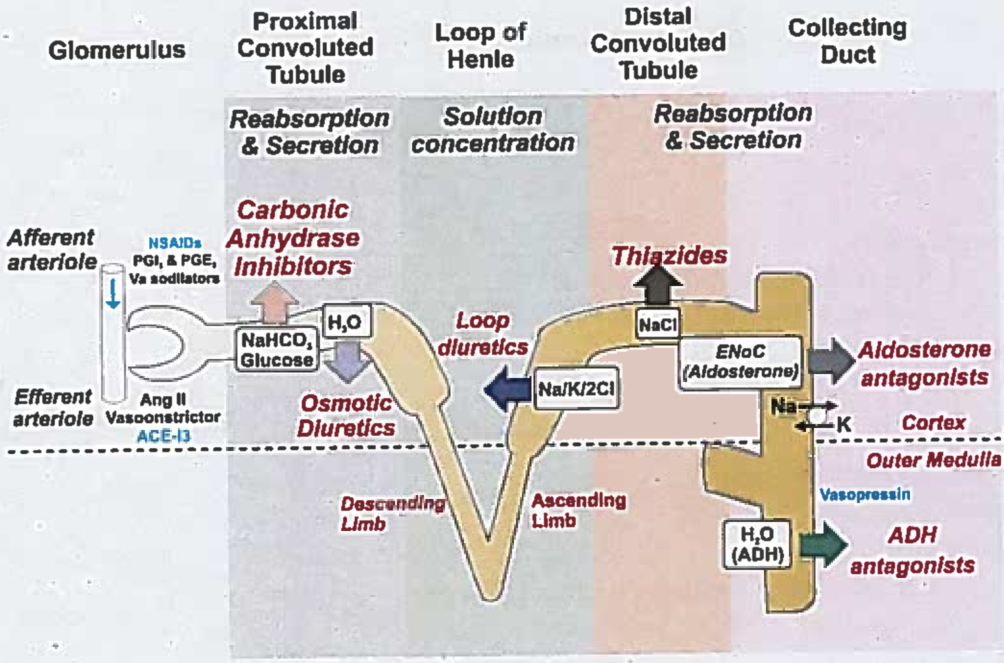
MNEMONIC: PaK-India Usually Never Gives Appreciation and Hate each other

PAH > K^+ (high-K^+ diet) > Inulin > Urea > Na^+ > Glucose, Amino acids, and HCO_3

Renal Regulation of NaCl, K^+, Urea, PO_4, Ca^{++}, Mg^{++}

	PCT	Loop Of Henle	Distal Tubule And Collecting Duct	Effect Of Hormone/ Drug
NaCl	**Early PCT:** • *Absorbs **67%** of Na+* and H2O by cotransport with glucose, amino acids, phosphate, and lactate • Na+ is also reabsorbed by counter transport via Na+–H+ exchange causing reabsorption of HCO3 **Late PCT** • Na+ - Cl cotransporter. **Site Of Glomerulotubular Balance** • *it means that even if GFR ↑ still it maintains constant fractional reabsorption (two-thirds, or 67%) of the filtered Na+ and H2O*	• in Thick ascending limb of the loop of Henle **25%** of the filtered Na+ is reabsorbed • Contains a Na+–K+–2Cl- cotransporter in the luminal membrane **Thick ascending limb** • *Impermeable to water so called diluting segment*	Together reabsorb **8%** of the filtered Na+. **Early DT:** • By Na+ - Cl cotransporter • *impermeable to water so called cortical diluting segment* **Late DT and collecting duct** • Principal cells→ reabsorb Na+ and H2O and secrete K+. • α-Intercalated cells secrete H+, or reabsorbs K+ by an H+, K+-ATPase	**Carbonic anhydrase I nhibitors (e.g.,** *acetazolamide) act àon the early PCTàåHCO3 reabsorption* **Loop Diuretics** *(furosemide), act son Thick ascending limb of the loop of Henle inhibit the Na+–K+–2Cl- cotransporter.* **Thiazide Diuretics** *early DT Inhibition of Na+–Cl–cotransport* **Principal Cellsà** *ADH and aldosterone* **α-Intercalated cellsà** *aldosterone*
K+	Reabsorbs 67% of the filtered K+ along with Na+ and H2O.	Reabsorbs 20% of the filtered K+. by the Na+–K+–2Cl- cotransporter	Depends on dietary K+ intake. • low-K+ diet (K+ depletion)→ K+ is reabsorbed by an H+, K+-ATPase in α-Intercalated cells • high K+ → secretes K+ by principal cells	**Causes of ↑ Distal K+ Secretion:** • *High-K+ diet* • *Hyperaldosteronism* • *Alkalosis* • *Thiazide diuretics* • *Loop diuretic* **Causes of ↓ Distal K+ Secretion:** • *Hypoaldosteronism* • *Acidosis* • *Low-K+ diet* • *K+-sparing diuretics*

Urea	50% reabsorbed	secreted here	impermeable to urea	
Phosphate	85% reabsorbed	no absorption	no absorption	PTHâreabsorption
Ca^{2+} and Mg^{2+}	• Proximal tubule and thick ascending limb reabsorb more than 90% of the filtered Ca2+ by passive processes that are coupled to Na+ reabsorption. • Mg2+ and Ca2+ compete for reabsorption • *So ↑ Ca2+ ↓ Mg2+ and vice versa*		**↑Ca2+ reabsorption** • PTH • Thiazide diuretics **↓Ca2+ reabsorption** • Loop diuretics	



Potassium Shifts

Shifts K+ Into Cell (Causing Hypokalemia)	Shifts K+ Out Of Cell (Causing Hyperkalemia)
	Mnemonic: DO LAβSS
	Digitalis (blocks Na+/K+ ATPase)
Hypo-osmolarity	*HyperOsmolarity*
	Lysis of cells (e.g., crush injury, tumor lysis syndrome)
Alkalosis	*Acidosis*
β- agonist	*β-blocker*
Insulin (INsulin shifts K+ INto cells)	*High blood Sugar (insulin deficiency)*
	Succinylcholine (↑ risk in burns/muscle trauma)

Hormones Acting on Kidneys

Hormone	Actions on the Kidneys
PTH	• ↓Phosphate reabsorption (proximal tubule) • ↑Ca^{2+} reabsorption (distal tubule) • Stimulates 1α-hydroxylase (proximal tubule)
ADH	• ↑H_2O permeability (late distal tubule and collecting duct principal cells)
Aldosterone	• ↑Na^+ reabsorption (distal tubule principal cells) • ↑K^+ secretion (distal tubule principal cells) • ↑H^+ secretion (distal tubule α-intercalated cells)
ANP	• ↑*GFR* *↓Na^+ reabsorption*
Angiotensin II	• ↑Na^+–H^+ exchange and HCO_3^- reabsorption (proximal tubule)

Buffers

- **Extracellular buffer**
  - *Major extracellular buffer is bicarbonate (HCO_3)*
  - *Minor extracellular buffer is Phosphate (most important urinary buffer)*
- **Intracellular Buffers**
  - *Major intracellular buffer is protein (hemoglobin deoxyhemoglobin > oxyhemoglobin)*
  - Other intracellular buffer are Organic phosphates (e.g., AMP, ADP, ATP, 2,3-diphosphoglycerate [DPG])

Kidney Endocrine Functions

- **Erythropoietin**
  - Released by interstitial cells in peritubular capillary bed *in response to hypoxia.*
  - *Stimulates RBC proliferation in bone marrow.*
- **Calciferol (vitamin D)**
  - *PCT cells convert 25-OH vitamin D3 (inactive) to* $\xrightarrow{\text{1a-hydroxylase}}$ *1, 25-(OH) 2 vitamin D3 (calcitriol, active form).*
- **Prostaglandins**
  - *Paracrine secretion vasodilates the afferent arterioles to* ↑ RBF.
  - Mnemonic (**PDA**---Prostaglandins Dilates Afferent arterioles)

Concentration and Dilution of Urine

Production of Concentrated Urine	Production of Dilute Urine
• Is also called hyperosmotic urine, in which urine osmolarity > blood osmolarity. Is produced when *circulating ADH levels are high (e.g., water deprivation, volume depletion, SIADH).* • **Mechanism** · Water deprivation Increases plasma osmolarity Stimulates osmoreceptors in anterior hypothalamus Increases secretion of ADH from posterior pituitary Increases water permeability of late distal tubule and collecting duct Increases water reabsorption Increases urine osmolarity and decreases urine volume Decreases plasma osmolarity toward normal	• Is called hypoosmotic urine, in which urine osmolarity < blood osmolarity. Is produced *when circulating levels of ADH are low (e.g., water intake, central DI) or when ADH is ineffective (nephrogenic DI).* • **Mechanism** · Water intake Decreases plasma osmolarity Inhibits osmoreceptors in anterior hypothalamus Decreases secretion of ADH from posterior pituitary Decreases water permeability of late distal tubule and collecting duct Decreases water reabsorption Decreases urine osmolarity and increases urine volume Increases plasma osmolarity toward normal

Acidosis and Alkalosis

- Normal values

pH	7.35-7.45 (below 7.35 is acidic and above 7.45 is alkalosis)
Co_2	35-45 (less than 35 alkalosis, and above 45 acidosis)
HCO_3	22-26below 22 acidosis and above 26 alkalosis)

Analysis (5 steps)

Step-1	• Is the pH normal? • Look for pH value first and compare whether it is acidic or alkalotic
Step-2	• Is the CO_2 normal? • Look for CO_2 value first and compare whether it is acidic or alkalotic
Step-3	• Is the HCO3 normal? • Look for HCO_3 value first and compare whether it is acidic or alkalotic
Step-4	• Match the CO_2 or the HCO_3 with the pH? • Look for the value which is making the pH acidic or basic suppose if pH is acidic and respiratory value is also acidic then the cause is respiratory acidosis and vice versa
Step-5	• Does the CO2 or the HCO3 go the opposite direction of the pH? Next step looks for the value which goes in opposite direction, suppose if pH is acidic, CO2 is acidic, and you have made the diagnosis of respiratory acidosis. HCO3 is basic, this means compensation has been done and diagnosis will be, respiratory acidosis with metabolic alkalosis.

Example: 1

- ✓ pH: 7.27 acidotic
- ✓ CO2: 53 acidotic
- ✓ HCO3: 24 normal

The full diagnosis fo r this blood gas is: **"Uncompensated respiratory acidosis"**

Example: 2

- ✓ pH: 7.60 alkalotic
- ✓ CO2: 37 normal
- ✓ HCO3: 35 alkalotic

The full diagnosis for this blood gas is **"Uncompensated metabolic alkalosis".**

Disorder		pH	Primary defect	Compensatory response	Magnitude of compensation
Metabolic Acidosis		↓	↓HCO3⁻	↓PCO_2	• The pCO_2 will ↓ by 1 mmHg *for every* 1 mmol /l for ↓ in HcO_3-
Metabolic Alkalosis		↑	↑HCO3⁻	↑PCO_2	• The pCO_2 will↑ by 1 mmHg *for every* 1 mmol/l for ↑ in HCO_3-
Respiratory Acidosis	Acute	↓	↑PCO_2	↑HCO3⁻	• *The HCO_3 will↑by 1 mmol/l for every 10 mmHg↑in pCO2 above 40 mmHg*
	Chronic	↓	↑PCO_2	↑HCO3⁻	• *The HCO_3 will↑by 4 mmol/l for every 10 mmHg↑in pCO2 above 40mmHg.*
Respiratory Alkalosis	Acute	↑	↓PCO_2	↓HCO3⁻	• *The HCO_3 will ↓ by 2 mmol/l for every 10 mmHg ↓ in pCO2 below 40 mmHg*
	Chronic	↑	↓PCO_2	↓HCO3⁻	• *The HCO_3 will ↓ by 5 mmol/l for every 10 mmHg ↓ in pCO2 below 40 mmHg*

Serum Anion Gap and Examples of Acid Base Disorders

Metabolic Acidosis

- The Anion Gap is used for the evaluation of metabolic acidosis to determine the presence of unmeasured anions.
- *The anion gap is the difference between primary measured* ***Cations*** *(Na+) and the primary measured* ***anions*** *(Chloride Cl- and bicarbonate HCO3-) in serum.*
  - ***Anion gap = Na^{+} − (Cl^{-} + $HCO3^{-}$)***
- Examples

↑nion gap > 12 mEq/L	Normal anion gap 8-12 mEq/L
MUDPILES: • **M**ethanol (formic acid) • **U**remia • ***Diabetic ketoacidosis*** • **P**ropylene glycol • **I**ron tablets or INH • **L**actic acidosis • **E**thylene glycol • ***Salicylates (late)***	**HARDASS:** • **H**yperalimentation • **A**ddison disease • ***Renal tubular acidosis*** • ***Diarrhea*** • **A**cetazolamide • **S**pironolactone • **S**aline infusion

Metabolic Alkalosis

- ***Loop diuretics***
- Vomiting
- Antacid use
- Hyperaldosteronism

Respiratory Acidosis

- **Airway obstruction**
- Acute lung disease
- **Chronic lung disease**
- ***Opioids, sedatives***
- Weakening of respiratory muscles

Respiratory Alkalosis

- Hysteria
- Hypoxemia (e.g., high altitude)
- ***Salicylates (early)***
- Tumor
- ***Pulmonary embolism***

Electrolyte Disturbances

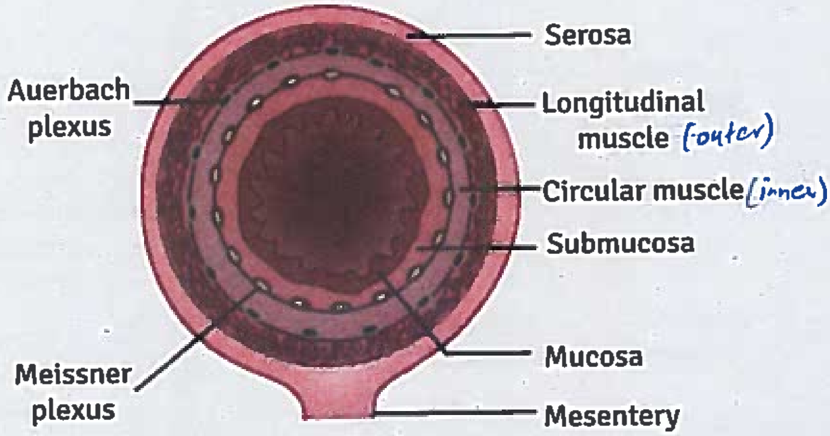
Electrolyte	Low Serum Concentration	High Serum Concentration
Sodium	• Nausea, malaise, stupor, coma, *seizures*	• Irritability, stupor, coma
Postassium	• *U waves & flattened T waves* on ECG, • Arrhythmias, muscle cramps, weakness	• *Wide QRS & peaked T waves* on ECG, Arrhythmias, muscle weakness
Calcium	• *Tetany*, seizures, *QT prolongation,* • Twitching (eg, Chvostek sign), spasm (eg, Trousseau sign)	• Stones (renal), bones (pain), groans (abdominal pain), psychiatric overtones (anxiety, altered mental status)
Magnesium	• Tetany, *torsades de pointes,* hypokalemia, hypocalcemia	• ↓DTRs, lethargy, bradycardia, hypotension, cardiac arrest.
Phosphate	• Bone loss, osteomalacia (adults), rickets (children)	• Renal stones, *metastatic calcifications,* hypocalcemia

Chapter 5: Gastrointestinal

Wall of GI TRACT (MSMS)

- Four layers which are (from inside out)

Mucus layer	• Innermost layer and has three layers of structures 1. Epithelial lining • Specialized in different parts of the GI tract for secretion or absorption • *The inner surface of mouth, surface of tongue, inner surface of pharynx and esophagus have→stratified squamous epithelial cells.* • *Stomach, small intestine and large intestine has→columnar epithelial cells* 2. Lamina propria • Contain fibro blasts, macrophages, lymphocytes and eosinophils 3. Muscularis mucosa • A thin layer of smooth muscle fibers. It is absent in mouth and pharynx. It is present from esophagus onwards.
Submucus layer	Blood vessels, ***Submucosal nerve plexus (MeiSSner), Secretes fluid***
Muscular layer	• ***Includes Myenteric nerve plexus (Auerbach), causes Motility*** (b/w the circular & longitudinal layers of stomach) • Lips, cheeks and wall of pharynx→skeletal muscle fibers. • The esophagus→skeletal and smooth muscle fibers. • Stomach and intestine→smooth muscle fibers • Smooth muscle fibers in stomach are arranged in three layers; Inner oblique layer, Middle circular layer, Outer longitudinal layer. • Smooth muscle fibers in the intestine are arranged in two layers; Inner circular layer and Outer longitudinal layer (Inner) **Circular muscle layer** →Contraction causes a decrease in diameter of the lumen of the GI tract. (outer) **Longitudinal layer** →Contraction causes shortening of a segment of the GI tract
Serous or fibrous layer.	• Outermost layer of the wall of GI tract



Nerve supply of GI tract

- GI tract has two types of nerve supply
  - Intrinsic nerve supply- Enteric Nervous System
  - Extrinsic nerve supply

Intrinsic nerve supply- Enteric Nervous System	• Controls all the secretions and movements of GI tract and has two major networks called; Auerbach plexus and Meissner plexus.
	• Auerbach plexus (Myenteric plexus)
	  · Situated in between the inner circular and the outer longitudinal muscle layer.
	  · ***Primarily controls the motility of the GI smooth muscle.***
	• Meissner plexus (Submucosal plexus)
	  · ***Primarily controls secretion and blood flow.***
	  Situated in between the muscular layer and submucosal layer

Extrinsic nerve supply	• Parasympathetic nervous system
	  · ***Is usually excitatory on the functions of the GI tract.***
	  · Is carried via the vagus and pelvic nerves.
	  · Vagus nerve innervates→the esophagus, stomach, pancreas, and upper large intestine.
	  · Pelvic nerve innervates→the lower large intestine, rectum, and anus.
	• Sympathetic nervous system
	  · ***Usually inhibitory on the functions of the GI tract.***

GI Hormones

- Divided into three categories

1. **Hormones**

Substance	Source	Stimulus For Secretion	Action

• **Gastrin**	• G cells (antrum of stomach, duodenum)	• Secreted by
		  · Small peptides and amino acids e.g. phenylalanine and tryptophan
		  · Distention of stomach
		  · Vagus via gastrin-releasing peptide (GRP)
		• Inhibited by
		  H+ in stomach
		  somatostatin
			• Stimulates growth of gastric mucosa
			• ↑Gastric H+ secretion *(Gastrin↑acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells).*

• **CCK**	• I cells (duodenum, jejunum)	• Small peptides and amino acids • Fatty acids	• *Stimulates contraction of gallbladder and relaxation of sphincter of Oddi* • *↑Pancreatic enzyme and HCO_3 secretion* • ↑Growth of exocrine pancreas/ gallbladder (letting work to be done in duodenum & Jejunum) • *Inhibits gastric emptying*
• **Secretin**	• S cells of duodenum	• H+ in duodenum • Fatty acids in duodenum	• ↑Pancreatic HCO3 secretion • ↑Biliary HCO3 secretion • ↓Gastric H+ secretion

• **GIP**	• Duodenum and jejunum	• Fatty acids, amino acids, and oral glucose	• ↑Insulin secretion ↓Gastric H+ secretion

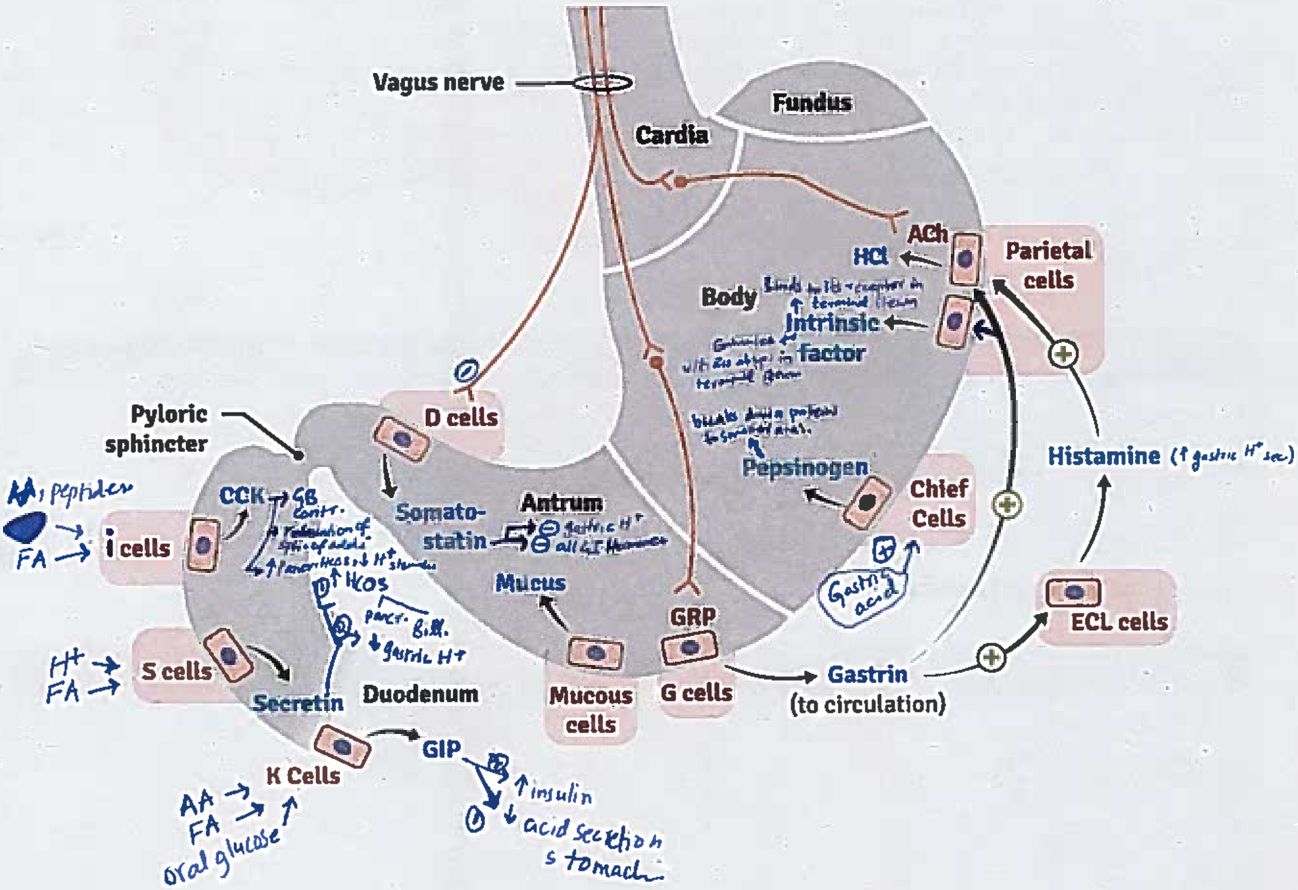
2. Paracrines

• **Somatostatin**	• ↑in response to H+ in the lumen ↓by vagal stimulation	• Inhibits gastric H+ secretion • Inhibits the release of all GI hormones.
• **Histamine**	• Secreted by ECL cells	• Increases gastric H+ secretion

3. Neurocrines

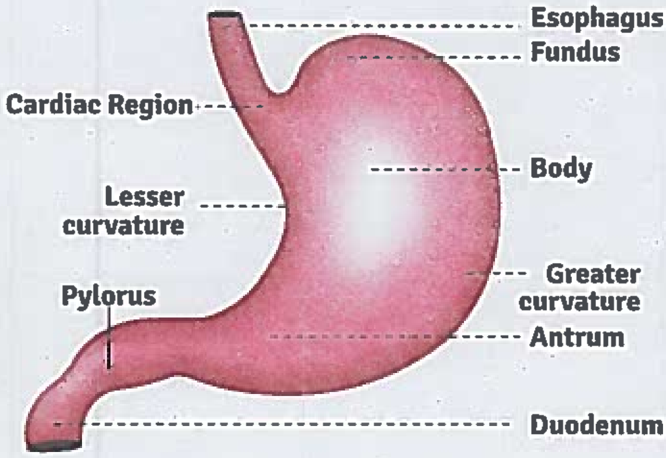
Vasoactive intestinal peptide (VIP).	(Same as secretin) ↑Pancreatic HCO3 secretion ↓Gastric H+ secretion	**VIPoma**—non-α, non-β islet cell pancreatic tumor that secretes VIP. **W**atery **D**iarrhea, **H**ypokalemia, and **A**chlorhydria (**WDHA** syndrome).
GRP (bombesin)	Released from vagus nerves that innervate the G cells.	• Stimulates gastrin release from G cells.

Appetite	*Leptin Lowers appetite* • *Ghrelin Gains appetite* • *Ghrelin Gains appetite*



Gastrointestinal motility

- Circular muscleContraction causes a decrease in diamε ter of the lumen of the GI tract,
- Longitudinal muscleContraction causes shortening of ε segment of the GI tract
- **Slow waves:**
  - Occurs spontaneously, originate in interstitial cells of Cajal, they are not true action potential but determine action potential
  - Mechanism:
    - *Depolarization (opening of Ca^{2+} channels) and repolarization (opening K+ channels),*
  - Frequency:
    - *Varies along the GI tract is lowest in the stomach (3 slow waves/min) and highest in the duodenum (12 slow waves/min).*
    - *Slow waves is not influenced by neural or hormonal input. However action potentials occurring on top of the slow waves is modified by neural and hormonal influences.*
- **Chewing:** Lubricates food, decreases size of particles
- **Swallowing:**
  - *Centre: medulla*
  - *Nerves involved: vagus and glossopharyngeal*
  - Sequence: nasopharynx, glottis and breathing closed food propelled into esophagus
- **Esophagus:**
  - Upper esophageal sphincters relaxes allows food peristalsis lower esophageal sphincter relaxes (via vagus nerve and hormones is VIP) food propelled into stomach.
- **Stomach:**
  - Includes fundus body and antrum.
  - Mixing waves occur controlled by slow waves, then some of weak peristaltic constrictor waves becomes strong and intense passed the food into duodenum called chyme.
  - Even during fasting, contractions (the "migrating myoelectric complex") occur at 90-minute intervals and clear the stomach of residual food. Motilin is the mediator of these contractions
  - Regulation of gastric emptying:
    - Gastric contractions ↑ by vagal stimulation and ↓ by sympathetic stimulation.



Inhibitors of Gastric Motility / Emptying	Stimulants of Gastric Motility / Emptying
• *Hormones: CCK, secretin, GIP.*	• *Gastrin*
• *Fat (via CCK), H+ in the duodenum and distention of duodenum*	• GRP
	• *Motilin*
	• Histamine

- **Small and large intestine**

Inhibitors of Intestinal Motility	Stimulants of Intestinal Motility
• *Sympathetic Stimulation*	• *Parasympathetic stimulation*
• Glucagon and Secretin.	• *CCK*
	• Gastrin
	• Motilin
	• Serotonin

Quick Review:

- *CCK is inhibitors of gastric motility but stimulant of intestinal motility*
- *Secretin is inhibitor of both gastric and intestinal motility*
- *Gastrin and Motilin is stimulatory for both gastric and intestinal motility*

Sequence of event in small intestine

Mixing contractions	• Back and forth movements of segments causes the food to mix without any forward movement of chyme.
Propulsive movements (peristalsis)	• By enteric nervous system. Contraction behind and relaxation in front of the bolus pushes the food forward. • ***Serotonin initiate the peristaltic reflex.***
Gastroileal reflex	• Presence of food in the stomach→↑peristalsis in the ileum and relaxation of the ileocecal sphincter. • As a result, the intestinal contents are delivered to the large intestine

- **Sequence of events in large intestine**

Proximal colon	• Proximal colon distended→the ileocecal sphincter contracts to prevent reflux into the ileum. • Segmentation contractions in the proximal colon mix the contents and are responsible for the appearance of haustra.
Distal colon	• In distal colon fecal material becomes semisolid (because most water absorption in proximal colon)d→pushed into rectum
Rectosphincteric reflex	• When rectum filled with fecal material→internal anal sphincter relaxes (rectosphincteric reflex) →when convenient external anal sphincter relaxed voluntarily
Gastrocolic reflex	• Presence of food in the stomach→↑the motility of the colon

Gastrointestinal Secretion

Salivary Secretions

Initial starch digestion by salivary amylase and initial TG's digestion by lingual lipase

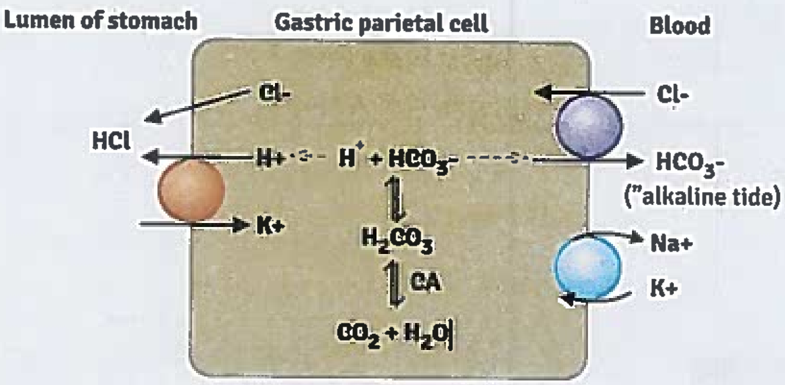
- Stimulated by: Sympathetic and parasympathetic (CN VII and IX) nervous system (not by GI hormones)
- Inhibited by: Anticholinergic drugs (e.g., atropine), Sleep and fear.
- Enzymes:
  - *Salivary amylase→Converts starch into maltose*
  - *Maltase→Converts maltose into glucose*
  - *Lingual lipase→Converts triglycerides of milk fat into fatty acids and diacylglycerol.*

Gastric secretions

Cell type	Secretes	Stimulated by	Inhibited by
Parietal cells	• Hcl	• *Gastrin* *Vagal stimulation (ACh)* *Histamine*	• *Atropine* *Omeprazole* *Cimetidine*
	• *Intrinsic factor*		
Chief cells	• Pepsinogen	• Vagal stimulation (ACh)	
G cells	• *Gastrin*	• Vagal stimulation (via GRP) • Small peptides	• *Inhibited by somatostatin or H+ in stomach*

Mechanism of Gastric H+ secretion

- Parietal cells secrete HCl into the lumen of the stomach and, concurrently, absorb HCO_3 into the bloodstream as follows
- In the parietal cells, CO_2 and $H_2O \xrightarrow[\text{by carbonic anhydrase}]{\text{Converted to}} H_2CO_3$ →which becomes H+ and HCO_3.
- H+ is secreted into the lumen of the stomach by the H+-K+ pump (H+, K+-ATPase). Cl^- is secreted along with H+; thus, the secretion product of the parietal cells is HCl.
- The HCO_3 produced in the cells is absorbed into the bloodstream in exchange for Cl– (Cl^-–HCO_3^- exchange).
- As HCO_3^- is added to the venous blood, the pH of the blood increases ("alkaline tide"). (Eventually, this HCO_3^- will be secreted in pancreatic secretions to neutralize H+ in the small intestine.)



Increases gastric H+ secretion	• *Hormones: Gastrin and Histamine* *Factors:* · *Vagal stimulation* · *Direct pathwayacting on parietal cells, neurotransmitter is ACh* · *Indirect pathwayvia gastrin neurotransmitter is GRP (not Ach)* · *Gastrinoma* · *Small bowel resection (removal of inhibition)* · *Systemic mastocytosis (elevated histamine levels)*
Decreases gastric H+ secretion	• ***Low pH*** *→negative feedback* • ***Drugs:*** *H2-antagonists, PPIs* • ***Hormones:*** *secretin, VIP, GIP, CCK and somatostatin* • ***Vagotomy:*** *(inhibits both direct and indirect pathway)* • ***Atropine:*** *inhibits direct pathway which uses Ach as a neurotransmitter*

Gastric Vs. Duodenal Ulcers

Gastric ulcers	Duodenal ulcers
• Major cause: H. pylori	• Major cause: H. pylori
• Deceased H+→because secreted H+ leaks back through the damaged gastric mucosa.	• Increased H+→Excess H+ is delivered to the duodenum, damaging the duodenal mucosa.
• *Most common area-- lesser curvature within the antrum*	• *Most common area- first portion of duodenum*
• Gastric ulcer pain Grows with food	• Duodenal ulcer pain Decreases with food
• Associated with increased risk of malignancy	• Virtually Never malignant
• *Hemorrhage→from erosion of left gastric artery*	• *Hemorrhage→(posterior>anterior)→from erosion of Gastroduodenal artery*

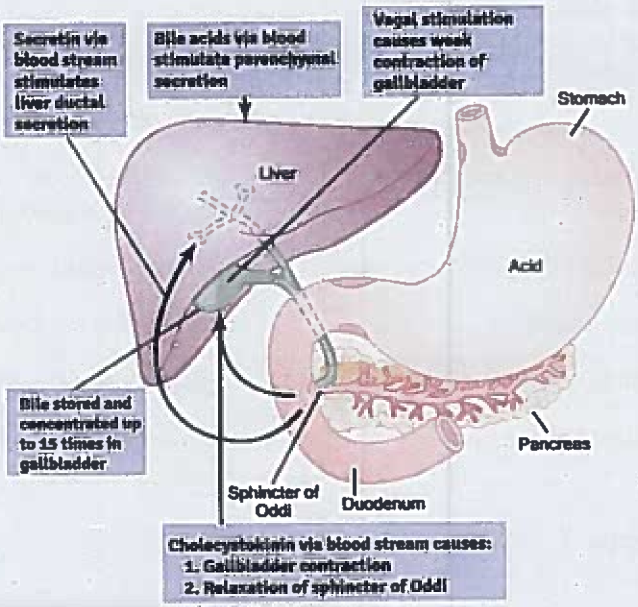
Pancreatic Secretions

- Isotonic fluid; contains
  - at low flow→Na+ & high Cl^-
  - and at high flow→Na+ & high HCO^{3-}

Enzymes	Function	Stimulated by	Notes
• **α-amylase**	• Starch digestion	• Secretin • CCK • ACh (via vasovagal reflex)	• *Trypsinogen converted to its active form trypsin by* ***enterokinase/ enteropeptidase****, a brush-border enzyme on duodenal and jejunal mucosa*
• **Lipases**	• Fat digestion		
• **Proteases**	• Protein digestion Includes trypsin, chymotrypsin, and elastase.		

Bile Secretions

Composition of Bile	1. Bile salts · Bile acid conjugated to glycine or taurine making them water soluble · Aid in intestinal absorption of lipids, by surrounding themselves around lipids, process called emulsification. 2. Phospholipids 3. Cholesterol and Bilirubin
Formation of Bile	Produced by hepatocytes then via hepatic ducts reach and stored in gall bladder, where it becomes concentrated Steps: 1. Cholesterol $\xrightarrow{\text{hepatocytes}}$ primary bile acids (cholic acid and chenodeoxycolic acid) 2. Primary bile acids $\xrightarrow{\text{bacteria in intestine}}$ secondary bile acids (deoxycholic acid and lithocholic acid) 3. Then bile acids conjugate with glycine or taurine to form bile salts 4. Electrolytes and H_2O are added to the bile.
Release of Bile	<u>CCK</u> • *Released in response to small peptides and fatty acids in duodenum Causes contraction of gall bladder and relaxation of sphincter of oddi to release bile*
Re-circulation of Bile Acids	• *Absorbed in terminal ileum where Na-bile acid co-transporter is present which recirculates it to liver* • After ileal resection, bile acids are not recirculated to the liver but are excreted in feces. The bile acid pool is thereby depleted, and fat absorption is impaired, resulting in steatorrhea



Digestion and Absorption of Nutrients

- *Carbohydrates, proteins, and lipids are digested and absorbed in the Small intestine.*
- The surface area for absorption in the small intestine is greatly increased by the presence of the brush border.

Nutrient	Digestion and absorption	Notes
Carbohydrates	• Carbohydrates must be digested to monosaccharides for absorption to occur. • Only monosaccharides (glucose, galactose, and fructose) are absorbed by enterocytes. • Glucose and galactose are taken up by SGLT-1 (Na+ dependent cotransport). • Fructose is taken up by facilitated diffusion • All are transported to blood by GLUT 2.	• *D-xylose absorption test: distinguishes GI mucosal damage from other causes of malabsorption.* • *Lactose intolerance results from the absence of brush border lactase*
Proteins	1. Digestion In Stomach: • Proteins [illegible] breaks the peptide bonds. 2. Digestion In Pancreas: • Digestion of protein is completed in the small intestine by the pancreatic enzymes trypsin, chymptrypsin, and carboxypeptidases Absorption: • Absorbed as free aminoacids, dipeptides, and tripeptides • Free aminoacids via Na+ dependent cotransport: • Dipeptides, and tripeptides via H+ dependent cotransport	• Pancreatic proteases include trypsin, chymotrypsin, elastase, carboxypeptidase A, and B. • They are secreted in inactive forms that are activated in the small intestine as follows: 1. **Trypsinogen is activated to trypsin by a brush border enzyme, enterokinase.** 2. Trypsin then converts chymotrypsinogen, proelastase, and procarboxypeptidase A and B to their active forms. **(Even trypsinogen is converted to more trypsin by trypsin)** Trypsinogen $\xrightarrow{\text{Enterokinase}}$ Trypsin Trypsinogen $\longrightarrow$ Trypsin
Lipids	• In stomach→ Lingual lipases helps in digestion and CCK slows emptying to allow more time for digestion in pancreas bile acids emulsify it and pancreatic lipases helps in digestion	

Absorption of Electrolytes and H2O

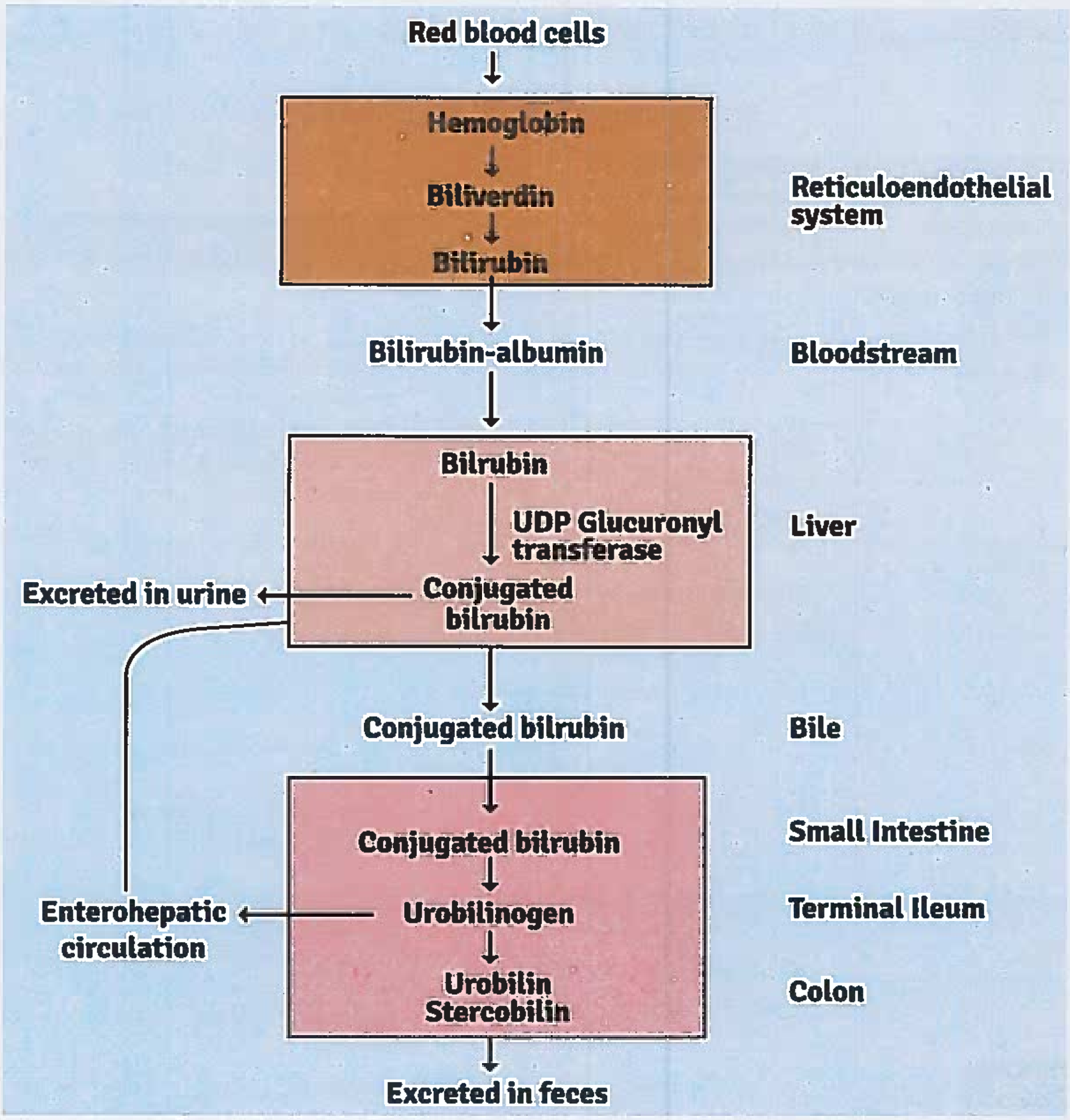
NaCl	• In small intestine and colon by following mechanism ◦ Passive diffusion (through Na+ channels) ◦ Na+-glucose or Na+-amino acid cotransport ◦ Na+-Cl- cotransport ◦ Na+-H+ exchange
K+	• Absorbed in small intestine Actively Secreted in colon
H2O	• 80% in small intestine • 10% in large intestine • 10% excreted in faeces.

Absorption of Vitamins and Minerals

Vitamins/minerals	Absorption	Notes
Fat soluble vitamins (A, D, E, K)	• *Absorbed with lipids in small intestine*	
Folate	• *Absorbed in small intestine*	• *Vitamin B12 absorption and folate absorption are Na+-independent,* • *But all seven of the remaining water-soluble vitamins are absorbed by carriers that are Na+-cotransporters.*
Calcium	• *Absorbed in small intestine, requires active form of Vitamin-D i.e., 1, 25-dihydroxycholecaciferol which is produced by kidneys.*	
Iron	• *Absorbed as Fe^{2+} in duodenum*	• Free Fe^{2}+→binds to apoferritin transported to blood. • Transported to liver for storage • From liver to bone marrow for synthesis of Hb.
Vitamin B_{12}	• *Absorbed in terminal ileum, requires intrinsic factor that is present in stomach*	• *Gastrectomy→loss of parietal cells→pernicious anemia* • *Ileectomy→loss of absorption→pernicious anemia*

Bilirubin

- Hemoglobin is degraded to bilirubin by the reticuloendothelial system.
- Bilirubin is carried in the circulation bound to albumin.
- In the liver, bilirubin is conjugated with glucuronic acid via the enzyme UDP glucoronyl transferase.
- A portion of conjugated bilirubin is excreted in the urine, and a portion is secreted into bile.
- In the intestine, conjugated bilirubin is converted to urobilinogen, which is returned to the liver via the enterohepatic circulation, and urobilin and stercobilin, which are excreted in feces.


Red blood cells
Hemoglobin
Biliverdin
Bilirubin
Reticuloendothelial system
Bilirubin-albumin
Bloodstream
Bilrubin
UDP Glucuronyl transferase
Liver
Excreted in urine
Conjugated bilrubin
Conjugated bilrubin
Bile
Conjugated bilrubin
Small Intestine
Enterohepatic circulation
Urobilinogen
Terminal Ileum
Urobilin Stercobilin
Colon
Excreted in feces

Chapter 6: Endocrinology

Hormones

Source	Hormones
Hypothalamus	• Thyrotropin-releasing hormone (TRH) • Corticotropin-releasing hormone CRH • Gonadotropin-releasing hormone (GnRH) • Growth hormone-releasing hormone (GHRH) • Somatotropin release-inhibiting hormone (SRIF /somatostatin) • Prolactin-inhibiting factor (PIF/ dopamine)
Anterior Pituitary	• Growth hormone (GH)[redacted] • Thyroid stimulating hormone (TSH) • Adrenocorticotropic hormone (ACTH) • Follicle stimulating hormone (FSH) • Luteinizing hormone (LH) • Prolactin **Basophilic** • *(FLAT) = FSH, LH, ACTH, TSH.* **Acidophilic** • *GH, Prolactin*
Posterior Pituitary	• Antidiuretic hormone (ADH) • Oxytocin
Thyroid Gland	• Thyroxine (T4) Triiodothyronine (T3) Calcitonin
Parathyroid Gland	• ~~Thyroxine (T4)~~ ~~Triiodothyronine (T3)~~ ~~Calcitonin~~ • Parathyroid hormone
Pancreas	• βcells→Glucagon (peripheral) • β cells→Insulin (central) • δ cells→Somatostatin (interspersed)
Adrenal Cortex	• Mineralocorticoids→Aldosterone • Glucocorticoids→Cortisol • Sex hormones→Androgens, Estrogen, Progesterone
Adrenal Medulla	• Adrenaline (Epinephrine) • Noradrenaline (Norepinephrine) • Dopamine

Hormones Secreted by Gonads and Other Glands:

Source	Hormones
Testis	• Testosterone • Dihydrotestosterone and Androstenedion.
Ovaries	• Estrogen and Progesterone
Pineal gland	• Melatonin
Thymus	• Thymosin and Thymin
Kidney	• Erythropoietin • Renin • 1,25dihydroxycholecalcifero (calcitriol) • Prostaglandins
Placenta	• Human chorionic gonadotropin (HCG) • Human chorionic somatomammotropin • Estrogen and Progesterone

Hypothalamic-Pituitary Hormones

Hormone	Function	Clinical Notes
CRH	• ↑ACTH, MSH, β-endorphin	• ↓in chronic exogenous steroid use.
Dopamine	• ↓prolactin, TSH↓	• *Dopamine antagonists (e.g., antipsychotics) can cause galactorrhea due to hyperprolactinemia.*
GHRH	• ↑GH	• Analog (tesamorelin) used to treat HIV-associated lipodystrophy
GnRH	• ↑FSH, LH	• Suppressed by hyperprolactinemia. Tonic GnRH suppresses HPG axis (Hypothalamic-pit-gonadal axis) Pulsatile GnRH leads to puberty, fertility
Prolactin	• ↓GnRH (↓estrogen in women ↓testosterone in men)	• *Pituitary prolactinoma à amenorrhea, Osteoporosis, hypogonadism, galactorrhea*
Somatostatin (octreotide is an analogue) which	• ↓GH, TSH↓	• Analogs (e.g., octreotide) used to treat acromegaly.
TRH	• ↑TSH, prolactin↑	• ↑TRH (e.g., in 1°/2° hypothyroidism) may increase prolactin secretion galactorrhea.

→ prolactinoma is un-common cause of osteoporosis. There is Hypogonadism, alteration normal GnRH pulsatile secretion leading to: ↓estrogen women & ↓testosterone in men thereby causing ↓bone mass.

Chemistry of Hormones

- Hormones are chemical messengers, synthesized by endocrine glands.
- Based on chemical nature, hormones are classified into three types.

Hormones Secreted by Gonads and Other Glands:

Steroid hormones	Protein hormones	Amine hormones
Derivatives of cholesterol	Formed by ER as preprohormone→cleaved into prohormone→transported to Golgi apparatus where it is cleaved to form hormone.	Derivatives of tyrosine.
Aldosterone Cortisol Testosterone Dihydrotestosterone Estrogen Progesterone	**(FLAT PIG)** FSH LH ACTH TSH Prolactin Parathormone Insulin Growth hormone (GH) Glucagon	Thyroxine (T4) Triiodothyronine (T3) Adrenaline (Epinephrine) Noradrenaline (Norepinephrine) Dopamine.

Mechanism of Hormone Action

cAMP mechanism *(FLAT ChAMP*	***Ip$_3$* (inositol tri-phosphate) mechanism (GOAT HAG**	***Steroid hormone mechanism* (PET CAT on TV**	***Tyrosine kinase activation* (Includes Growth Products)**	**cGMP (BAD GraMPa)**
cAMP	IP3	St.	Tk	cGMP
FSH	*GnRH*	*Progesterone*	*Insulin*	*BNP*
LH	*Oxytocin*	*Estrogen*	*IGF-1*	*ANP*
ACTH	*ADH*	*Testosterone*	*Growth hormone*	*EDRF (NO)*
TSH	*TRH*	*Cortisol*	*Prolactin*	
CRH	*Histamine (V_1 receptor)*	*Aldosterone*		
hCG	*Angiotensin-II*	*Thyroid hormones*		
ADH	*Gastrin*	*Vitamin D*		
PTH				

Pituitary Gland (Hypophysis)

- *Lies in sella turcica*

Ant. Pituitary (adenohypophysis)	Post. Pituitary (neurohypophysis)
• *Ectodermal in origin and arises from Rathke's pouch.*	• *Neuroectodermal in origin and arises from hypothalamus.*
• Hormones from hypothalamus are transported to anterior pituitary through Hypothalamo-hypophyseal portal blood vessels.	• Hormones from hypothalamus to posterior pituitary are transported by nerve fibers.

Ant. Pituitary

(FLAT PiG)→FSH, LH, ACTH, TSH, Prolactin and GH
FSH, LH, ACTH and TSH are discussed later in this chapter

1. **Growth hormone (Somatotropin)**
   - Homologous with prolactin and human placental lactogen released in pulsatile fashion.
   - Regulation
     - Secretion is Increased by:
       - *Hypothalamus via **GHRH** stimulates the synthesis and secretion of growth hormone Secretion is increased by **deep sleep**, exercise, puberty, and **hypoglycemia.***
     - Secretion is decreased by
       - Somatostatin (inhibits secretion of growth hormone by blocking the response of the anterior pituitary to GHRH),
       - Somatomedins (it inhibits the secretion of growth hormone by acting directly on the anterior pituitary and by stimulating the secretion of somatostatin from the hypothalamus.),
       - Obesity, **hyperglycemia**, and pregnancy.
   - Actions:

     ↓glucose uptake (diabetogenic), ↑lipolysis, ↑protein synthesis in muscle – ↑in lean body mass

2. **Prolactin**
   - Secretion is increased by estrogen (OCPs, pregnancy), breast feeding, dopamine antagonists (most antipsychotics).
   - *Secretion is decreased by dopamine*, Dopamine agonists (e.g., bromocriptine—can be used in treatment of prolactinoma) and by prolactin itself via negative feedback

     Actions:
     - *Milk production and breast development (along with estrogen), ↓GnRH (↓spermatogenesis and ovulation)*

Post. Pituitary

1. ADH
   - Originates in the supraoptic nuclei of the hypothalamus.

     Regulation:
     - *Secretion is increased by ↑Serum osmolarity, Volume contraction, **Nausea (powerful stimulant).***
     - Secretion is decreased by ↓Serum osmolarity and Ethanol
   - Actions:
     - ↑the H_2O permeability of the late distal tubules and collecting ducts ↑H_2O absorption less water in urine (concentrated urine).

2. **Oxytocin**
   - Originates in the paraventricular nuclei of the hypothalamus.

     Regulation: Suckling, sight and sound of the baby releases oxytocin

     Actions:
     - *Ejection of milk*
     - *Contraction of uterus during pregnancy* (Oxytocin can be used to induce labor and reduce postpartum bleeding)

Thyroid gland

- Thyroid hormones are tri-iodothyronine (T3) and thyroxine (T4)
- *Transported in blood by combining with plasma proteins, most of which is bound to thyroxine-binding globulin (TBG)*
- T4 is 90% and T3 is 10%.
- T4 is converted to T3 by iodinase
- *T3 is more active than T4.*
- Composed of
    - **Follicles**→major constituent of which is thyroglobulin that contains thyroid hormones
    - **Parafollicular © cell**→ present b/w thyroid follicles which secrete calcitonin, concerned with calcium metabolism.

In Hepatic Failure: plasma proteins↓, TBG↓→↓total thyroid hormones, but normal levels of free hormone

In Pregnancy: TBG↑→↑total thyroid hormone, but normal levels of free hormones (i.e., clinically euthyroid)

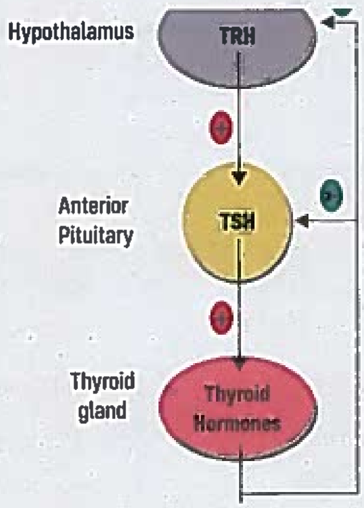
Formation

- 4 steps

1. Thyroglobulin is synthesized from tyrosine in the thyroid follicular cells,
2. Iodide trapping / iodide pump/ Na^+- I^- cotransport
    - Active transport of iodide into thyroid follicular cells is called iodide trapping for incorporation into thyroid hormones
    - Inhibited by thiocyanate.
3. Oxidation of iodide (I^-) to iodine (I_2)
    - Accelerated by peroxidase enzyme and inhibited by propylthiouracil
4. Organification of I_2
    - Tyrosine + I_2 mono-iodotyrosine (MIT)
    - MIT + I_2 DI-iodotyrosine (DIT)
    - MIT + DIT tri-iodothyronine (T_3)
    - DIT + DIT tetra-iodothyronine (T_4 or thyroxine)

Regulation

- Hypothalamus secretes TRH→which acts on ant. Pituitary which releases TSH→acts on thyroid releases T3 and T4→which in turn inhibits TSH secretion by acting on ant. Pituitary

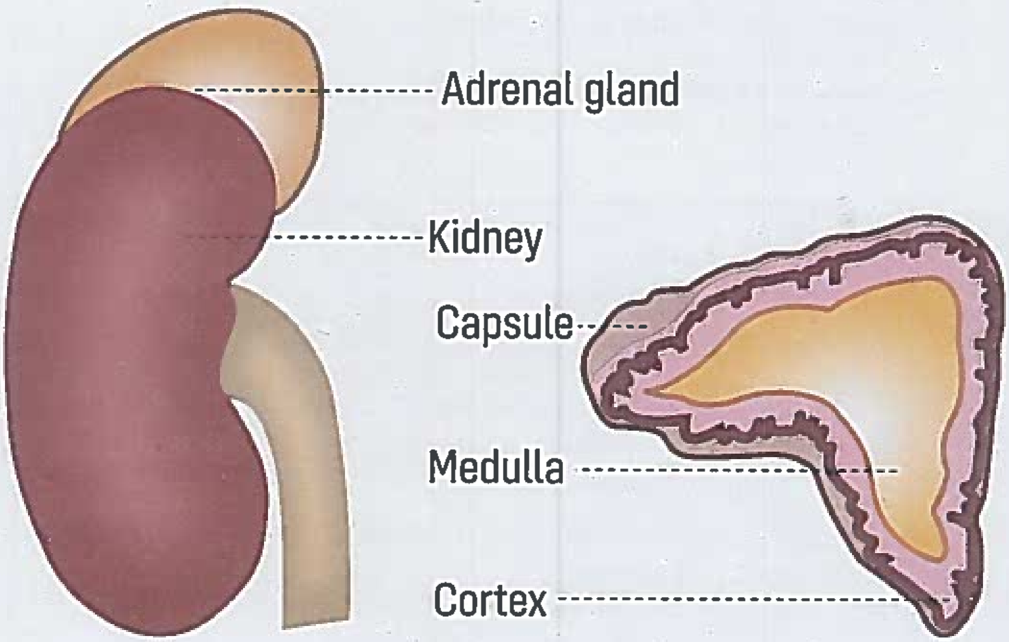


Action

- *Bone formation (along with growth hormone), bone maturation (thyroxin changes chondrocyte into osteocyte)*
  CNS maturation (deficiency causes mental retardation).
  Sympathetic effect→↑HR and stroke volume (high output heart failure) ,↑BMR, ↑Gluconeogenesis,↑glycogenolysis,↑lipolysis. The overall effect is catabolic—so as to meet the increase body requirement.

Adrenal Glands

- Lies at superior poles of two kidneys.
- Divided into adrenal cortex and adrenal medulla.
- Adrenal cOrtex→derived from mesOdermOuter→portion 80% of gland.
- Adrenal medulla derived from neural crest→inner portion→20% of gland



Adrenal Cortex (Adrenocortical Hormones)

- Adrenocortical hormones are steroids in nature, hence the name 'corticosteroids'. Based on their functions, corticosteroids are classified into three groups:
  - Mineralocorticoids
  - Glucocorticoids
  - Sex hormones (androgens).
- Consist of 3 layers from outside to inside.

Parts	Hormone Class	Hormone Produced
Zona Glomerulosa	Mineralocorticoids	Aldosterone
Zona Fasciculata	Glucocorticoids	Cortisol
Zona Reticularis	Androgens	DHEA (dehydroepiandrosterone) and Androstenedione.

Mnemonic: GFR corresponds with Salt (mineralocorticoids), Sugar (glucocorticoids), and Sex (androgens).

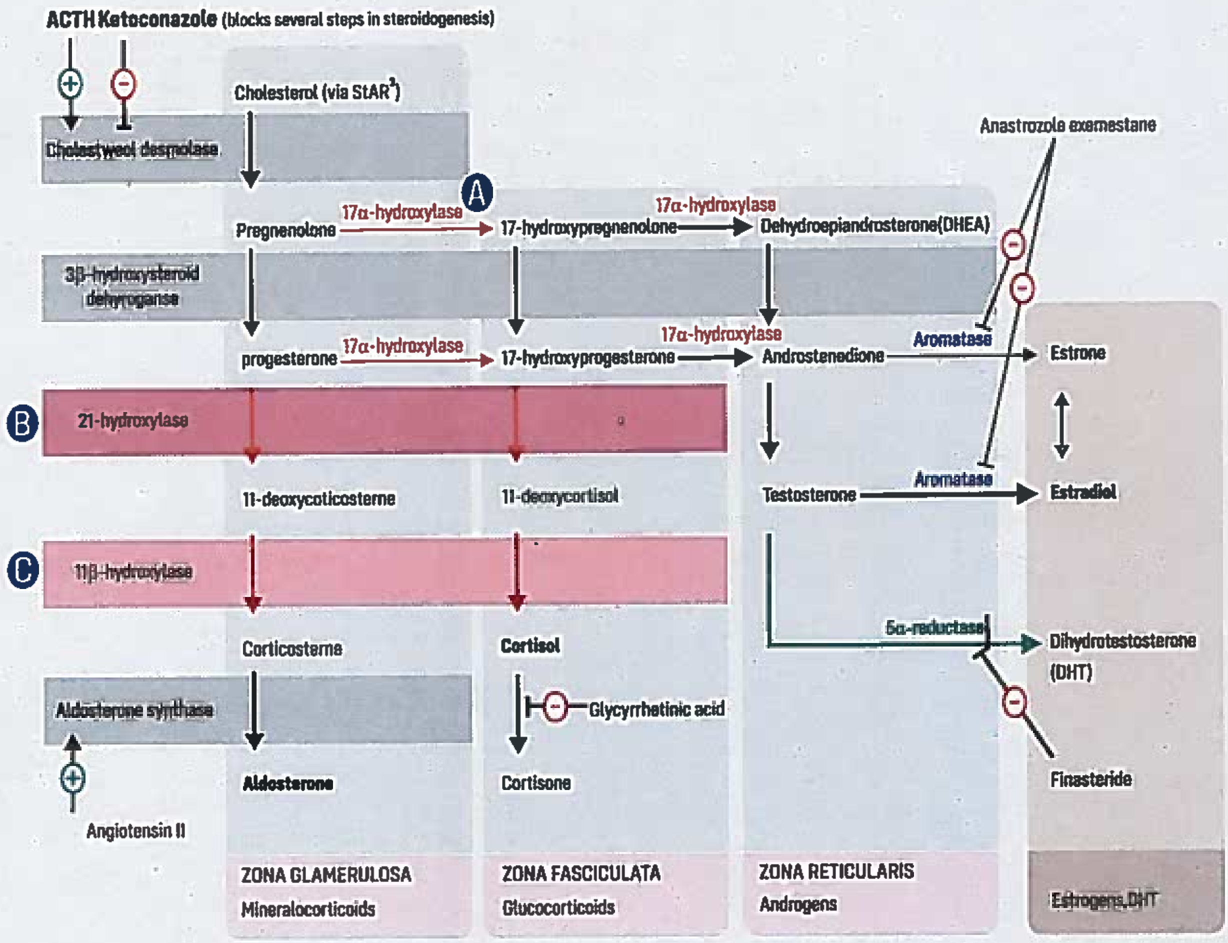
"The deeper you go, the sweeter it gets."

Synthesis of Adrenocortical hormones

- *All adrenocortical hormones are steroid in nature and are synthesized mainly from cholesterol.*

Enzyme Deficiency and Presentation

Enzyme Deficiency	Mineralocorticoids	Cortisol	Sex Hormones	BP	K+	Labs	Presentation
17α-hydroxylase	↑	↓	↓	↑	↓	• ↓Androstenedione	XY: ambiguous genitalia, undescended testes XX: lacks 2° sexual development
21-hydroxylase	↓	↓	↑	↓	↑	• ↑Renin Activity ↑ 17-Hydroxy progesterone	Most common Presents in infancy (salt wasting) or childhood (Precocious puberty) XX: virilization
11β-hydroxylase	• ↓Aldosterone • ↑11-Deoxycorticosterone (results in ↑BP)	↓	↑	↑	↓	• ↓Renin Activity	XX: virilization



Adrenal Cortex Hormones

Mineralocorticoids (Aldosterone)	Glucocorticoids (Cortisol)
• Act on the minerals (electrolytes), particularly sodium and potassium	• *Exhibits **circadian rhythm** (24-hour periodicity)→ For those who sleep at night, cortisol levels are highest just before waking (≈8 am) and lowest in the evening (≈12 midnight)*

Regulation (Mineralocorticoids)

- ACTH
- Renin-angiotensin-aldosterone system
  - ↓ECF VOLUME→↓renal perfusion pressure→activates renin secretion.
  - Renin causes conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE).
  - Angiotensin II→↑aldosterone.
  - Aldosterone increases renal Na^+ reabsorption, thereby restoring extracellular fluid (ECF) volume and blood volume to normal (shown in fig below)
- Hyperkalemia
  - It↑aldosterone secretion. Aldosterone ↑renal K^+ secretion, restoring serum [K^+] to normal.
  - *K^+ ions is the most effective stimulant for aldosterone secretion*

Regulation (Glucocorticoids)

- Hypothalamic -pituitary-cortex relationship
  - Hypothalamus release CRH (Corticotropin releasing hormone)→acts on Anterior pituitary releases ACTH→which acts on all zones of adrenal cortex→ and along with other hormones also ↑ cortisol level
- Negative feedback control by cortisol
  - Excess Cortisol level inhibits the secretion of CRH from the hypothalamus and the secretion of ACTH from the anterior pituitary by negative feedback
  - The dexamethasone suppression test is based on the ability of dexamethasone (a synthetic glucocorticoid) to inhibit ACTH secretion.
  - Test variants:

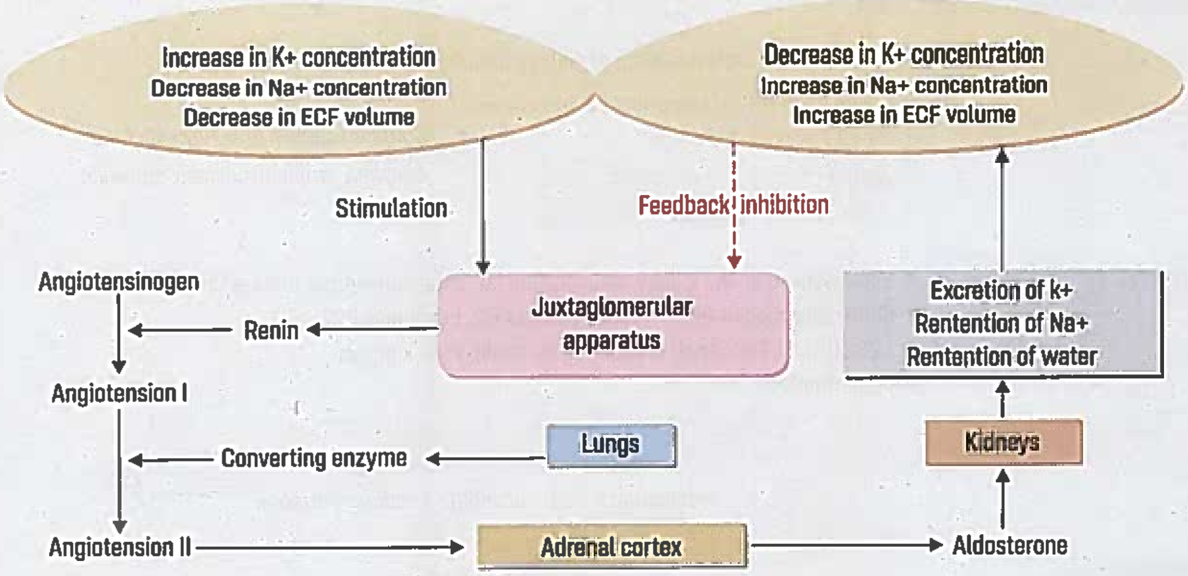
Normal Persons	ACTH-Secreting Tumors	Adrenal Cortical Tumors
Low-dose dexamethasone inhibits ACTH and cortisol secretion.	Low-dose dexamethasone does not inhibit cortisol secretion but high-dose dexamethasone does	Neither low- nor high-dose dexamethasone inhibits cortisol secretion.

Actions (Mineralocorticoids)

- *↑Renal Na^+ reabsorption (via principal cells)*
- *↑ Renal K^+ secretion (via principal cells)*
- *↑Renal H^+ secretion (via α-intercalated cells)*

Actions (Glucocorticoids)

- **Cortisol is a A BIG FIB.**
- ↑ Appetite
- ↑ Blood pressure: Upregulates α1-receptors on arterioles →↑sensitivity to vasoconstrictor effect of norepinephrine
- ↑ Insulin resistance (diabetogenic)
- *↑Gluconeogenesis, lipolysis, and proteolysis (i.e.↓glucose utilization)*
- ↓Fibroblast activity (poor wound healing, ↓collagen synthesis, ↑ striae)
- ↓Inflammatory and immune responses:
  - Inhibits production of leukotrienes and prostaglandins
  - Blocks histamine release from mast cells
  - Blocks IL-2 production
- *Bone formation (↓osteoblast activity)*



Endocrine Pancreas

CellsHormone	Stimulus for secretion	Action	Overall effect on blood levels
Alpha cells $\boxed{\text{Glucagon}}$ **(cAMP mechanism)**	• ↓Blood glucose • ↑Amino acids • CCK • Norepinephrine, epinephrine, ACh	GLUCAGON • *↑Glycogenolysis* • *↑Gluconeogenesis* • *↑Lipolysis And Ketoacid Production*	• ↑ Glucose • ↑ Fatty Acid • ↑ Ketoacid
Beta cells Insulin (tyrosine kinase receptor) TK	• ↑Blood glucose • ↑Amino acids • ↑Fatty acids Glucagon • GIP • Growth hormone • Cortisol	INSULIN • ↑glucose uptake into cells and glycogen formation • *↓glycogenolysis and gluconeogenesis* • *↑protein synthesis* • *↑fat deposition and decreases lipolysis* • *Increases K+ uptake into cells*	• ↓Glucose • ↓Amino Acid • ↓Fatty Acid • ↓Ketoacid • Hypokalemia
Delta cells→ somatostatin	*Inhibits secretion of insulin, glucagon and gastrin* of somatostatin		

Note:

- **Brain vs. RBC's**
  - Brain utilizes glucose for metabolism normally and ketone bodies during starvation.
  - RBCs utilize glucose because they lack mitochondria for aerobic metabolism.
- **Insulin-Independent Glucose Uptake:** Mnemonic: **BRICK- LE**
  - Brain, RBCs, Intestine, Cornea, Kidney, Liver, Exercising skeletal Muscles
- The factors which increase insulin would decreases glucagon and vice versa
  Both functions opposite to each other
  Insulin down regulates its own receptors in target tissue i.e.
  - oInsulin receptors are↑in starvation
  - ↓in obesity (type 2 DM)

Parathyroid Hormone

Source	• *Synthesized and secreted by chief cells of parathyroid gland*	
Regulations	• ↓serum Ca2+↑PTH secretion and vice versa ↑serum Po4↑PTH secretion ↓ *Serum Mg2+↑PTH secretion.* ↓↓*Serum Mg2+↓PTH secretion.*	• *Common causes of ↓Mg2+ include diarrhea, aminoglycosides, diuretics, alcohol*
Actions	• ↑Bone resorption and kidney reabsorption (at distal convoluted tubules) of Ca^{2+} ↑Bone resorption of PO_4,↓reabsorption of PO_4 in kidneys PCT. ↑1,25-$(OH)_2$ D_3 (calcitriol) production by stimulating kidneys Overall effect→ • *↑Serum Ca2+ (major hormone for regulation of Ca2+)* *↓Serum PO4 and↑urine PO4.* • ***Mnemonic: (PTH)*** *Phosphate Trashing Hormone*	

Calcitonin

Source	• Parafollicular cells (**C cells**) of thyroid.	• *Calcitonin opposes actions of PTH.* • Not important in normal Ca2+ homeostasis
Regulations	• ↑serum Ca2+ calcitonin secretion	
Actions	↓Bone resorption of Ca2+. ↓*Serum Ca2+* and keeps it in bones.	

Vitamin D

Source	• Sun, fish, cheese	• Inactive forms: • Cholecalciferol • *25 hydroxycholecalciferol* • *24,25 hydroxycholecalciferol* • Active form: • *1,25-$(OH)_2$ D_3* • *Converted to its active form in kidneys by 1α-hydroxylase.*
Regulations	• ↑PTH,↓serum ca2+,↓serum Po4↑1,25-$(OH)_2$ D_3 ↑1,25-(OH)2 D3 inhibits its own production by negative feedback	
Actions	• ↑absorption of intestinal as well as renal Ca2+ and PO_4→enhances bone mineralization	• Deficiency causes • *In children→Rickets* *In adults→Osteomalacia*

Calcium homeostasis

40% of total calcium→bound to plasma proteins (albumin).
60% of total calcium→not bound to proteins→free/ionized calcium, which is active form.

Normal Ca2+ balance	Positive Ca^{2}+ balance	Negative Ca^{2}+ balance
• Normal phenomena	• Seen in growing children	• Seen in pregnancy and lactation
• Intestinal absorption = urinary excretion	• Intestinal Ca^{2+} absorption more than urinary excretion. • Excess calcium is stored in growing bones	• Intestinal Ca^{2+} absorption less than urinary excretion • Deficit comes from maternal bones

Summary of hormones that regulate Ca^{2+}

PTH	• ↑Serum Ca^{2+}, ↓PO4.	
Vitamin D	• ↑Serum Ca^{2+}, ↑PO4.	
Calcitonin	• ↓Serum Ca^{2+}	• Secreted by Parafollicular cells of thyroid. • Can be used to treat hypercalcemia

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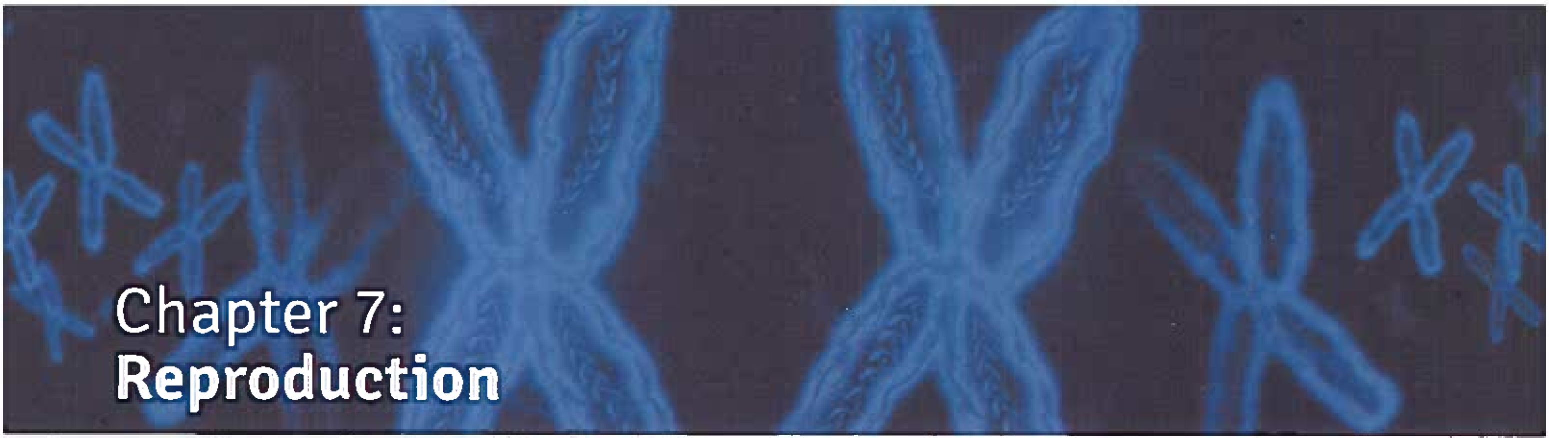


Chapter 7: Reproduction

Sexual Differentiation

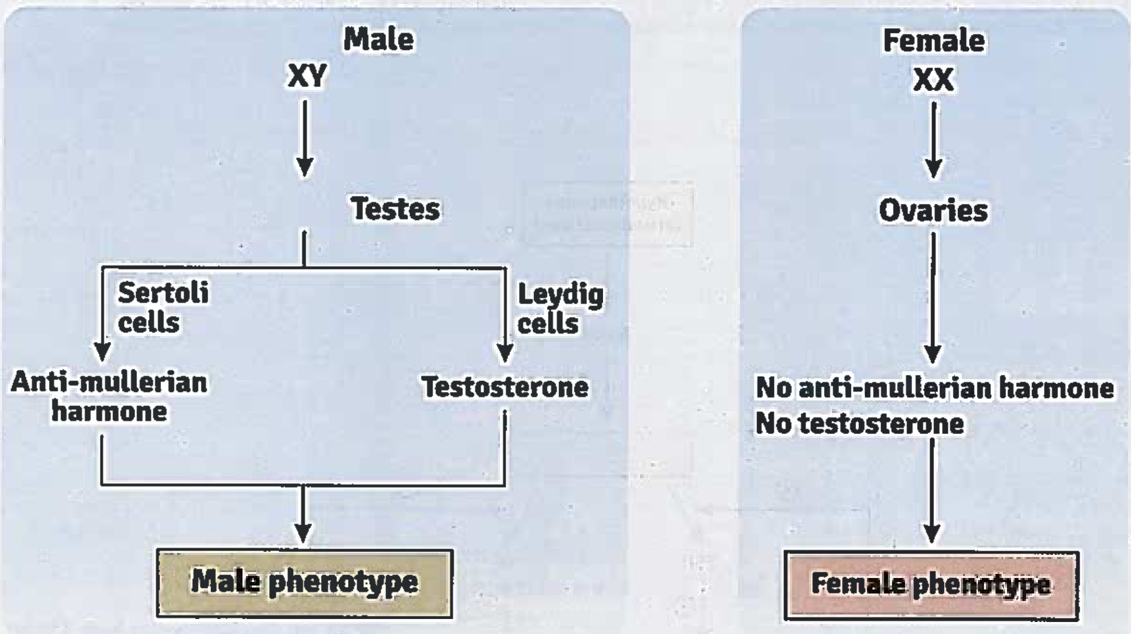
- Genetic sex is defined by the sex chromosomes, XY in males and XX in females.
- Gonadal sex is defined by the presence of testes in males and ovaries in females.
- Phenotypic sex is defined by the characteristics of the internal genital tract and the external genitalia.

Male Phenotype

- The testes of gonadal males secrete anti-mullerian hormone and testosterone.
- Testosterone stimulates the growth and differentiation of the wolffian ducts, which develop into the male internal genital tract.
- Anti-mullerian hormone causes atrophy of the mullerian ducts (which would have become the female internal genital tract).

Female Phenotype

- The ovaries of gonadal females secrete estrogen, but not anti-mullerian hormone or testosterone.
- Without testosterone, the wolffian ducts do not differentiate.
- Without anti-mullerian hormone, the mullerian ducts are not suppressed and therefore develop into the female internal genital tract.



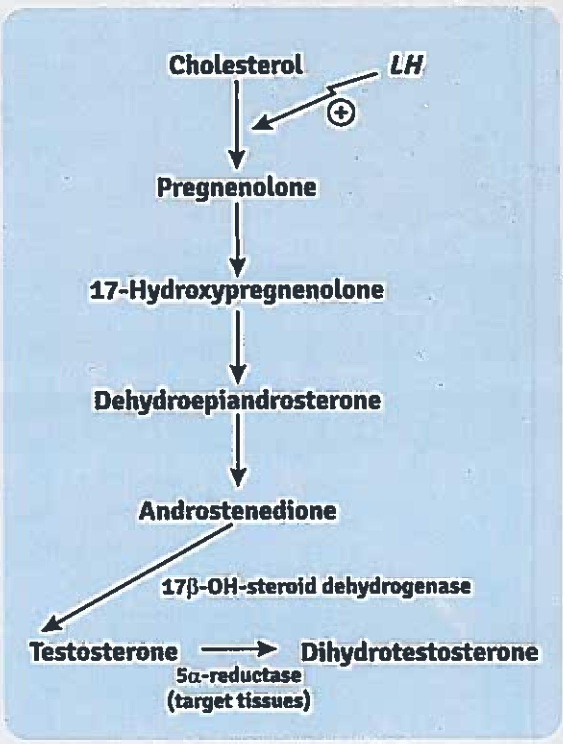
Male Reproduction

Components of the Vasculature

- **Testosterone is the major androgen synthesized and secreted by the Leydig cells.**
- Leydig cells do not contain 21β-hydroxylase or 11β-hydroxylase (in contrast to the adrenal cortex) and, therefore, do not synthesize glucocorticoids or mineralocorticoids.
- **LH** (in a parallel action to ACTH in the adrenal cortex) **increases testosterone synthesis by stimulating cholesterol desmolase,** the first step in the pathway.
- Accessory sex organs (e.g., prostate) contain 5α-reductase, which converts testosterone to its active form, dihydrotestosterone.

Note

- 5α-reductase inhibitors (finasteride) may be used to treat benign prostatic hyperplasia because they block the activation of testosterone to dihydrotestosterone in the prostate.



Regulation of Testes

Hypothalamic Control—GnRH

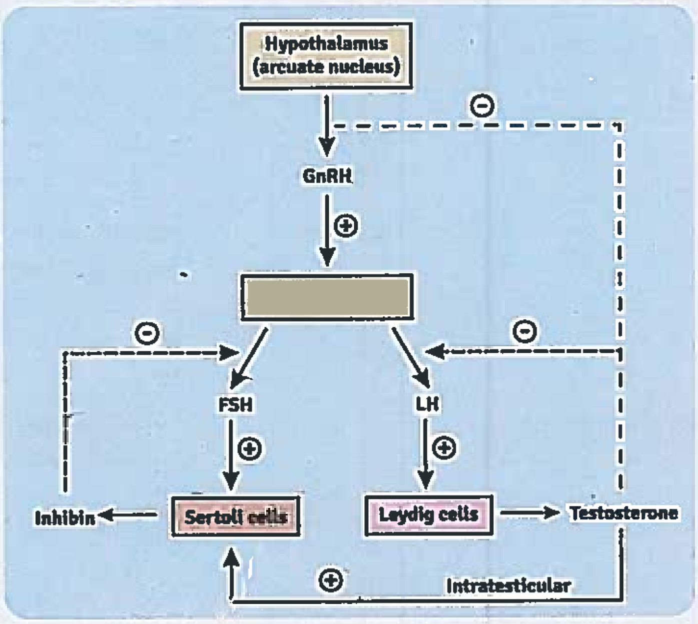
- Arcuate nuclei of the hypothalamus secrete GnRH into the hypothalamic-hypophyseal portal blood. GnRH stimulates the anterior pituitary to secrete FSH and LH.

Anterior Pituitary—FSH and LH

- FSH acts on the Sertoli cells to maintain spermatogenesis. The Sertoli cells also secrete inhibin, which is involved in negative feedback of FSH secretion.
- LH acts on the Leydig cells to promote testosterone synthesis. Testosterone acts via an intratesticular paracrine mechanism to reinforce the spermatogenic effects of FSH in the Sertoli cells.

Negative Feedback Control—Testosterone And Inhibin

- Testosterone inhibits the secretion of LH by inhibiting the release of GnRH from the hypothalamus and by directly inhibiting the release of LH from the anterior pituitary.
- Inhibin (produced by the Sertoli cells) inhibits the secretion of FSH from the anterior pituitary.

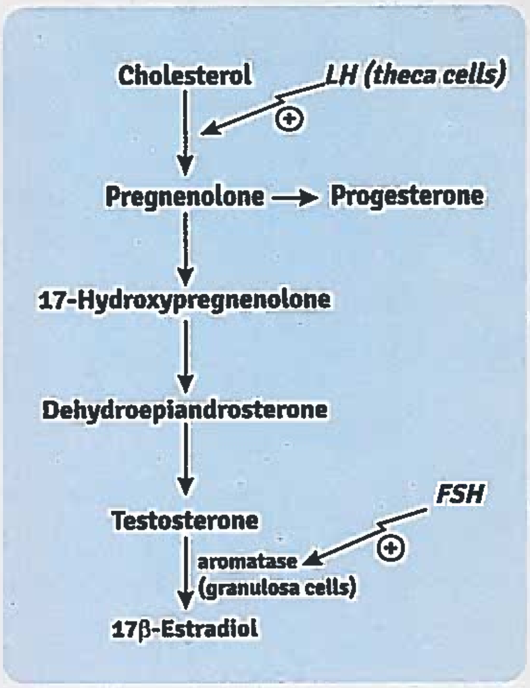


Female Reproduction

Synthesis of Estrogen and Progesterone

(ovary)

- Theca cells produce testosterone (stimulated at the first step by LH). Androstenedione diffuses to the nearby Granulosa cells, which contain 17β-hydroxysteroid dehydrogenase, which converts androstenedione to testosterone, and aromatase, which converts testosterone to 17β-estradiol (Stimulated by FSH).



Regulation of the Ovary

1. **Hypothalamic control—GnRH**
   - As in the male, pulsatile GnRH stimulates the anterior pituitary to secrete FSH and LH.
2. **Anterior lobe of the pituitary—FSH and LH**
   - FSH and LH stimulate the following in the ovaries:
     - Steroidogenesis in the ovarian follicle and corpus luteum
     - Follicular development beyond the antral stage
     - Ovulation
     - Luteinization
3. **Negative and positive feedback control by estrogen and progesterone**

Actions of Estrogen and Progesterone

Estrogen	Progesterone
• Has both negative and positive feedback effects on FSH and LH secretion	• Has negative feedback effects on FSH and LH
• Causes the development of the breasts and secondary sex characteristics	• Participates in development of the breasts
• Maintains pregnancy	• Maintains pregnancy
• Lowers the uterine threshold to contractile stimuli during pregnancy	• Raises the uterine threshold to contractile stimuli during pregnancy.
• Stimulates prolactin secretion (but then blocks its action on the breast).	

Variation in FSH and LH Levels over the Life Span (Male and Female)

- In childhood, hormone levels are lowest and FSH > LH.
- At puberty and during the reproductive years, hormone levels increase and LH > FSH.
- In senescence, hormone levels are highest and FSH > LH.

Estrogen Variations over the Life Span

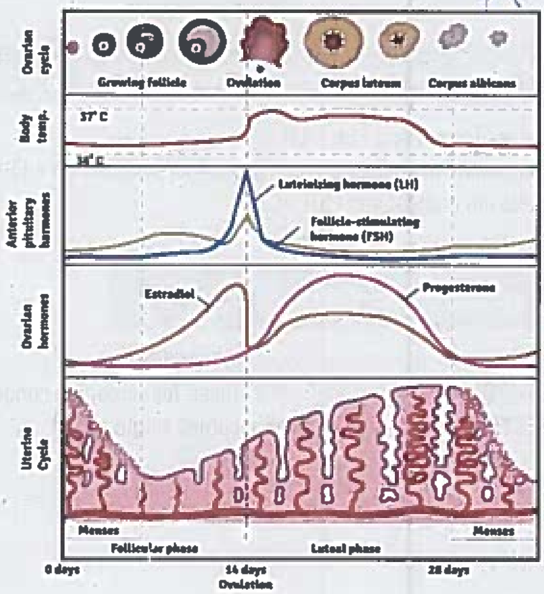
- Estrogen in Reproductive years (when a woman is like a doll) → ESTRADIOL
- Estrogen in pregnancy → ESTRIOL - (tri - mom, dad, child) (used for screening congenital abnormality).
- Estrogen in menopause: → ESTRONE --- (ONE - woman becomes single again)

Menstrual Cycle

Follicular Phase (Days 0 To 14)	• **Hormone responsible: FSH mainly and LH partly.** • A primordial follicle→primary follicle (under the influence of FSH & LH)→ mature Graafian follicle • LH and FSH receptors are up-regulated in theca and granulosa cells→ ↑Estrogen (Estradiol) • ↑ Estradiol levels causes proliferation of the uterus. • FSH and LH levels are suppressed by the negative feedback effect of estradiol on the anterior pituitary. • Progesterone levels are low.
Ovulation (day 14)	• **Hormone responsible: ↑ LH** • Occurs 14 days before menses, regardless of cycle length. Thus, in a 28-day cycle, ovulation occurs on day 14; in a 35-day cycle, ovulation occurs on day 21. • A burst of estradiol synthesis at the end of the follicular phase has a positive feedback effect on the secretion of FSH and LH (**LH surge**). • Ovulation occurs as a result of the estrogen-induced LH surge. • Estrogen levels decrease just after ovulation (but rise again during the luteal phase). • Cervical mucus increases in quantity; it becomes less viscous and more penetrable by sperm.

Luteal Phase (Days 14 To 28)
or secretory phase
	• The corpus luteum begins to develop, and it synthesizes estrogen and progesterone.
	• Vascularity and secretory activity of the endometrium increase to prepare for receipt of a fertilized egg.
	• Basal body temperature increases because of the effect of progesterone on the hypothalamic thermoregulatory center.
	• <u>**Fate Of Corpus Luteum:**</u>
	  ◦ If fertilization occur→↑corpus luteum size under the influence of hCG→secretes progesterone
	  ◦ If fertilization does not occur, the corpus luteum regresses→ called corpus Albicans→As a result, estradiol and progesterone levels decrease abruptly.

Menses (days 0 to 4)	• The endometrium is sloughed because of the abrupt withdrawal of estradiol and progesterone.



Pregnancy

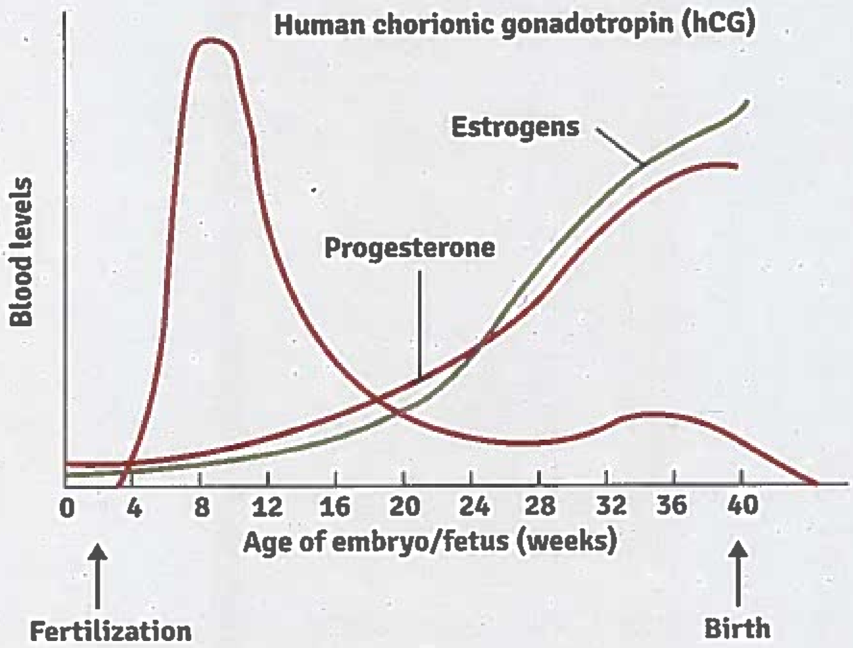
Fertilization	• If fertilization occurs, the corpus luteum is rescued from regression by human chorionic gonadotropin (HCG), which is produced by the placenta • Fertilization most commonly occurs in upper end of fallopian tube (the ampulla). • Occurs within 1 day of ovulation. • Implantation within the wall of the uterus occurs 6 days after fertilization. • Syncytiotrophoblasts (placenta) secrete hCG, which is detectable in blood 1 week after conception and on home test in urine 2 weeks after conception.
First Trimester	• The corpus luteum (stimulated by HCG) is responsible for the production of estradiol and progesterone. • Peak levels of HCG occur at gestational week 9 and then decline.
Second and Third Trimesters	• Progesterone is produced by the placenta. • Estrogens are produced by the interplay of the fetal adrenal gland and the placenta. • The major placental estrogen is estriol. • Human placental lactogen is produced throughout pregnancy. Its actions are similar to those of growth hormone and prolactin.

Gestational Age & Embryonic Age

Gestational Age	• Calculated from date of last menstrual period
Embryonic Age	• Calculated from date of conception (gestational age minus 2 weeks).

Physiologic Adaptations in Pregnancy:

- ↑ Cardiac output (↑ preload, ↓ afterload,
- ↑HR→↑ placental and uterus perfusion)
- Anemia (↑↑plasma, ↑ RBCs)
- Hypercoagulability (to ↓ blood loss at delivery)
- Hyperventilation (eliminate fetal CO2)



Lactation

- Estrogens and progesterone stimulate the growth and development of the breasts throughout pregnancy.
- Prolactin levels increase steadily during pregnancy because estrogen stimulates prolactin secretion from the anterior pituitary.
- Lactation does not occur during pregnancy because estrogen and progesterone block the action of prolactin on the breast.
- After labor, estrogen and progesterone levels decrease abruptly and lactation occurs.
- Lactation is maintained by suckling, which stimulates both oxytocin and prolactin secretion
  - Prolactin—induces and maintains lactation and ↓ reproductive function.
  - Oxytocin—assists in milk letdown; also promotes uterine contractions.
- Ovulation is suppressed as long as lactation continues because prolactin has the following effects:
  - Inhibits hypothalamic GnRH secretion.
  - Inhibits the action of GnRH on the anterior pituitary and consequently inhibits LH and FSH secretion.
  - Antagonizes the actions of LH and FSH on the ovaries

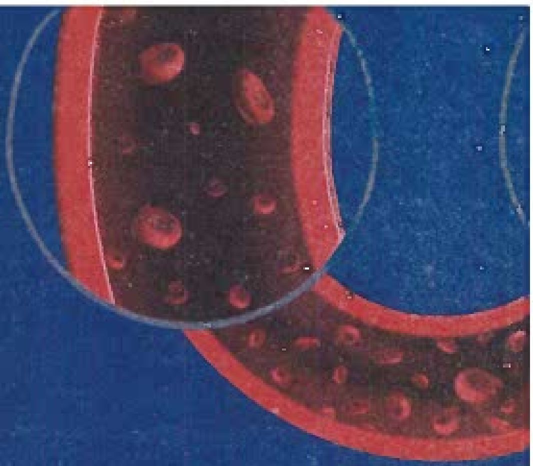
Remember mnemonic:	Progesterone is progestation.	Prolactin is prolactation.

Breast Milk

- **Breast milk is the ideal nutrition for infants < 6 months old.**
- Contains maternal immunoglobulins (Conferring passive immunity; mostly IgA), macrophages, lymphocytes
- Breast milk reduces infant infections and is associated with ↓risk for child to develop asthma, allergies, diabetes mellitus, and obesity.
- Exclusively breastfed infants require vitamin D supplementation.
- Breastfeeding ↓ maternal risk of breast and ovarian cancer and facilitates mother-child bonding.

Autonomic Innervation of the Male Sexual Response

Erection	Parasympathetic nervous system (pelvic nerve)
Emission	Sympathetic nervous system (hypogastric nerve)
Ejaculation	visceral and Somatic nerves (pudendal nerve)



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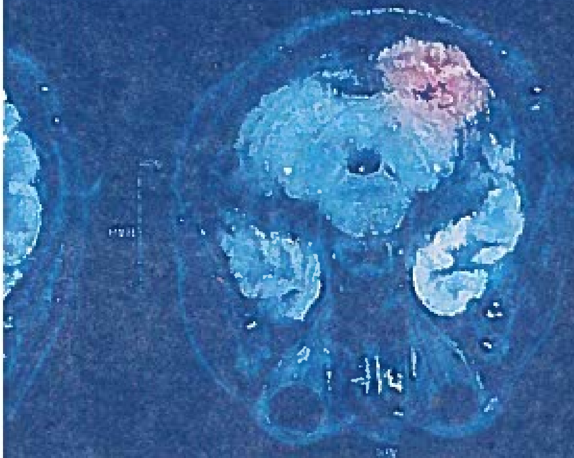
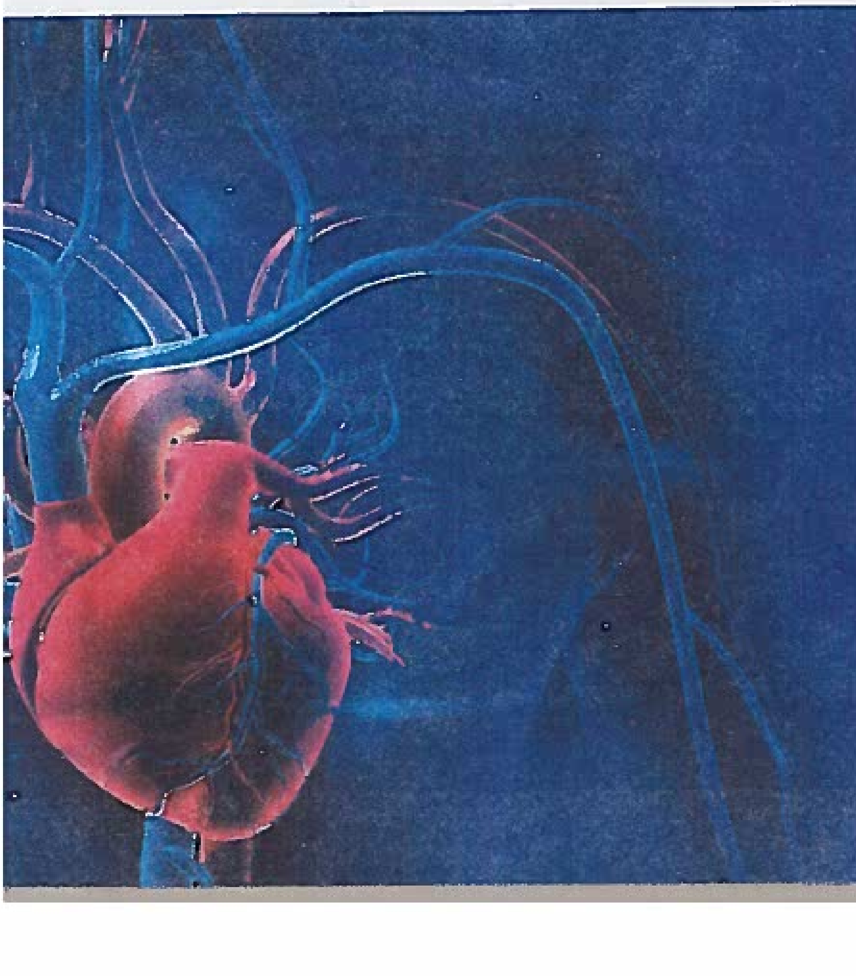
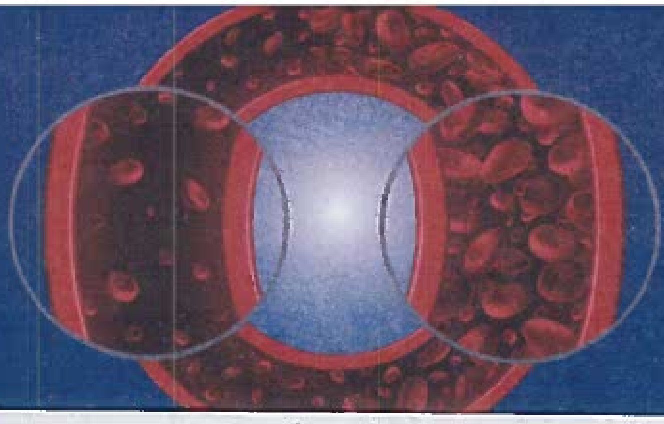


SPECIAL PATHOLOGY





Chapter 1: Anemia

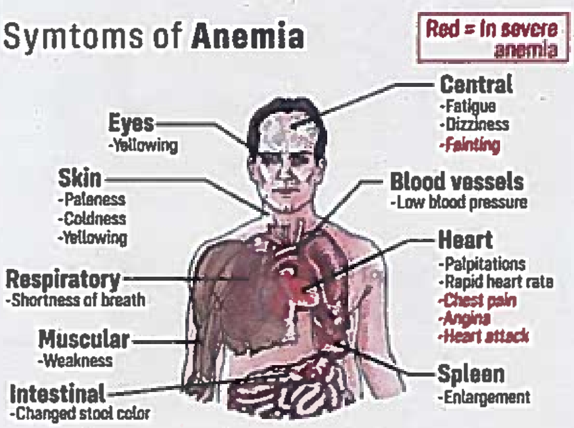
Characteristics of Cell Types

Characteristics of Cell Types	Disorder of leucocytes	Causes
Neutrophils • Multi-Lobed Nucleus • Acute inflammatory response cell. Increased in bacterial infections. Phagocytic. • Neutrophils spend 6-10 hours in the circulation • before being removed principally by spleen	Neutrophilia (↑ Count)	• Bacterial Infections (exception TB, typhoid) • Acute Inflammations such as Burns, MI • Asplenia • Leukemoid reaction • Stress/ exercise/ Corticosteroids
	Neutropenia (↓ Count)	• Hemolytic Anemia, Immune Thrombocytopenia • Viral infections (EBV, CMV, HIV) • Bacterial Infections (Brucella, TB) • Malaria • Leukemia, MDS. • Vit B12 Def.
Lymphocyte	Lymphocytosis (↑ count)	• Infection Usually viral; pertussis, toxoplasmosis • Serum sickness • Cardiac emergencies, trauma, status epilepticus, postsplenectomy • Autoimmune Rheumatoid arthritis (large granular lymphocytes), • Malignant Thymoma • Leukemia (ALL, CLL, others), lymphoma
Monocyte • Differentiates into macrophage in tissues.	Monocytosis (↑ count)	• Infection → Usually TB, SBE, Listeria, Brucella, Rickettsiae, fungi, parasites • Inflammation → IBD, sarcoidosis, collagen vascular diseases • Neoplasm → Hodgkin's disease, Leukemias, MPD, carcinomas

Eosinophil • Defense against helminthic (parasites) infections and increases in response to allergies	Eosinophilia (↑ count)	**Causes of eosinophilia = PACCMAN:** • **P**arasites • **A**sthma • Eosinophilic granulomatosis with polyangiitis (**C**hurg-Strauss syndrome) • **C**hronic adrenal insufficiency • **M**yeloproliferative disorders • **A**llergic processes • **N**eoplasia (eg, Hodgkin lymphoma)
Basophil • Basophil Mediates allergic reaction. • Densely basophilic granules contain heparin (anticoagulant) and histamine (vasodilator).	Basophilia (↑ count)	• it is uncommon, but can be a sign of myeloproliferative disease, particularly CML

Anemia

- Anemia is a decrease in red cell mass
- **Anemia of pregnancy is not anemia but rather is a manifestation of increased plasma volume.** With normal pregnancy blood volume increases, which results in a concomitant hemodilution. Although red blood cell (RBC) mass increases during pregnancy, plasma volume increases more, resulting in a relative anemia.



Classification

Microcytic (MCV <80 fL)	• Iron deficiency anemia • Thalassemia • Anemia of chronic disease • Lead poisoning • Sideroblastic anemia

Macrocytic (MCV >100 fL)	• <u>Megaloblastic macrocytic anemia (Hypersegmented neutrophils)</u>
	  · B12 deficiency anemia
	  · Folic acid deficiency anemia
	• <u>Non-megaloblastic macrocytic anemia (NO hypersegmented neutrophils)</u>
	  · Alcoholism
	  · Liver disease
	  · Hypothyroidism

Normocytic (MCV 80-100 fL)

- <u>Non- hemolytic anemia (reticulocyte count normal or ↓)</u>
  - Aplastic anemia
  - Anemia with chronic kidney disease
- <u>Intrinsic Hemolytic anemia (anemia with intrinsic cause, RC ↑)</u>
  - Hereditary spherocytosis (membrane defect)
  - G6PD, pyruvate kinase (enzyme deficiency)
  - Sickle cell anemia
  - Paroxysmal nocturnal hemoglobinuria
- <u>Extrinsic Hemolytic anemia (RC ↑)</u>
  - Autoimmune
  - Microangiopathic
  - Macroangiopathic
  - Infections

Microcytic Hypochromic Anemia

Iron deficiency anemia

- Most common anemia
- Dietary iron is absorbed in duodenum. Iron must be reduced i.e. Fe^{+2}
- Ascorbic acid reduces oxidized iron (Fe^{+3}) and is therefore important in iron reabsorption.
- Causes:
  - Dietary lack → children and elderly
  - Increased utilization → pregnancy, lactation and elderly
  - Impaired absorption → celiac disease, gastrectomy (gastric acid helps in iron reabsorption)
  - Blood loss → gastrointestinal blood loss, menorrhagia (most common in women)
- Clinical features:
  - Koilonychias (spoon shaped nails), angular cheilosis, Pica, atrophic glossitis
  - Plummer-Vinson syndrome:
- Triad of ("**P**lumbers" **DIE**).
  - <u>**D**ysphagia (Dysphagia for solids only)</u>
  - <u>**I**ron deficiency anemia, and</u>
  - <u>**E**sophageal webs.</u>
  - <u>Increased risk of esophageal squamous cell carcinoma</u>
- Lab findings:
  ↓ Serum iron, ↑ TIBC (↑ only in this anemia), ↓ ferritin (best test).

α-thalassemia

- Autosomal recessive disorder
- Characterized by ↓ synthesis of α-globin chains with relative excess of β-chains.
- α-chains four in number and expressed both pre-natally and post-natally
- α-thalassemia is due to gene deletions
- Types:
- Silent carrier →
  - (-/α α/α), deletion of one α-chain, asymptomatic.
- Alpha thalassemia trait→
  - (-/- α/α), deletion of 2 α chain, like β-thalassemia minor, mid anemia
- HbH disease →
  - (-/- -/α), characterized by $\boxed{\text{precipitation of β-chain}}$ tetramers, severe anemia
- Hydrops fetalis:
  - (-/- -/-), deletion of all 4 chains, most severe of all, incompatible with life
  - characterized by precipitation of $\boxed{\text{γ-chains tetramers}}$ (Hb barts)

b/c this shows in life, when β chains have come into production

β chain tetramers →

this even comes before life i.e in fetal stages of life, its so severe

γ chain tetramers →

fetus me HbF hota hai which is (~~[illegible]~~ α2γ2)

- Survival in early life is due to expression of gower-Hb.
- Signs of fetal distress 3rd trimester

Microcytic Hypochromic Anemia (continued)

β-thalassemia

Microcytic Hypochromic anemia

microcytic Hypochromic anemia, with target cells.

• circulating nucleated RBC's.

- Autosomal recessive disorder
- Characterized by ↓ synthesis of β-globin chains with relative excess of α-chains.
- β-chains four in number and expressed post-natally only, therefore anemia manifests 6-9 months after birth.
- β-thalassemia is due to point mutations (most commonly splicing mutations)
- β-thalassemia minor: (heterozygote, β0/β or β+/β—one mutated and one normal) → mildest form of disease
  - Mild anemia
  - Protective against falciparum malaria → minor.
  - Diagnosis confirmed by ↑HbA2 on electrophoresis
- β-thalassemia major: (Cooley's anemia, homozygous β0/β0 or β+/β+)
  - Severe microcytic anemia requiring blood transfusion (2° hemochromatosis).
  - Extra-medullary haematopoiesis:
    - Marrow expansion ("crew cut" on skull x-ray)
    - Skeletal deformities. "Chipmunk" facies
    - Leads to hepatosplenomegaly
    - ↑ Risk of parvovirus B19-induced aplastic crisis.
  - Diagnosis: ↑HbF (α2γ2). (MAJOR) (⊗ HbA)
  - HbF is protective in the infant and disease becomes symptomatic only after 6 months.

(↓)β normal, No β., Normal

massive erythropoiesis, all these tissues taking part in hematopoiesis.

β^+ = diminished (↓) β chains synthesis

β^0 = NO β chain synthesis absent.

HbA = ($\alpha_2\beta$

HbA2 ($A_2\delta_2$) Delta

HbF = ($A_2\gamma_2$) Gamma

Diagnosis

	HbA	HbA2	HbF
Normal	97-99%	1-3%	< 1%
Thalassemia minor/trait	80-95%	4-8%	1-5%
Thalassemia intermedia	0-30%	0-10%	6-100%
Thalassemia major	0-10%	4-10%	90-96%

Anemia of chronic disease

• Hepcidin is an acute phase reactant released in ACD, which locks Iron its storage sites, such that it then cant be used.

• Hepcidin can also suppress erythropoeitin levels.

$\boxed{\text{normocytic} \longrightarrow \text{microcytic}}$

- The serum iron is low (as in iron deficiency), but the TIBC is also low
- Most common anemia in malignancy and alcoholism, chronic inflammatory hospitalized patients
- Labs:
  - Peripheral blood
    - Mild: usually normocytic and normochromic
    - Moderate: may be microcytic and normochromic
    - Severe: may be microcytic and hypochromic
  - "Classic" serum iron indices
    - ↑Hepcidin ⟶ ↓ serum iron is low (as in iron deficiency), but the TIBC is also↓
    - Normal or ↑ Serum ferritin ⟵ Hepcidin. (so storage iron is ↑)
  - Bone marrow
    - Normal or increased iron stores
    - Decreased or absent staining for iron in erythroid precursors

Tr+. •EPO •cause erythropoietin in chronic disease

Lead poisoning

- ↓ Heme synthesis and ↑RBC protoporphyrin.
- High risk in old houses with chipped paint.
- Lead poisoning causes
  - Children—exposure to lead paint → mental deterioration.
  - Adults—environmental exposure (e.g., batteries, ammunition) →

- Symptoms of **LEAD** poisoning:
  - **Lead Lines on gingivae** (Burton lines) and on metaphyses of long bones D on x-ray.
  - **Encephalopathy** and **Erythrocyte basophilic stippling.**
  - **Abdominal colic** and sideroblastic Anemia.
  - **Drops**—wrist and foot drop. **Dimercaprol and EDTA are 1st line of treatment.**

Sideroblastic anemia

(Defective protoporphyrin synthesis)

$\boxed{\text{Heme} = \text{Iron} + \text{protoporphyrin}}$

↓

low protoporphyrin

↓

low Heme

↓

anemia.

can denature enzymes i-e ALAd & ferrochelatase

Iron trapped in mitochondria & keeps accumulating till it burst so serum iron ↑.

if ferritin is ↑, serum TIBC will be ↓.

% sat. will be ↑.

- Defect in heme synthesis within mitochondria. — Trapped iron.
- Iron is available but cannot incorporate it into Hb.
- Trapped iron forms a ring (ring Sideroblasts)
- Causes:
  - Hereditary: X-linked defect in δ-ALA (aminolevulinic acid) synthase gene. vit-B6 is a cofactor in this step.
  - Acquired: Chronic alcoholism (most common-mitochondrial toxin), lead, vitamin B6 deficiency. → damages prod. of protoporphyrin
- Ringed Sideroblasts (with iron-laden, Prussian blue-stained mitochondria) seen in bone marrow
- ↑ Iron, normal or ↓TIBC, ↑ferritin

ALAs requires B6 as a cofactor.

- Treatment
  - Depends on etiology
    - X-linked: high dose pyridoxine (vitamin B6, cofactor for δ-ALA synthase) in some cases
    - Acquired: EPO and G-CSF
    - Reversible: remove precipitating cause
  - Supportive transfusions for severe anemia

Microcytic Anemia Quick Summary

	Ferritin	Serum Iron	TIBC	Transferrin saturation	Blood film
Iron Def. Anemia	↓↓	↓	↑	↓	Hypochromic, microcytic
Anemia of chronic disease	Normal/↑	↓	↓	Normal	Normocytic or microcytic
Sideroblastic anemia	Normal/↑	↑	Normal or ↓TIBC	Normal/↑	Dual population Basophilic stippling
Thalassemia	Normal/↑	Normal/↑	Normal	Normal/↑	Hypochromic, microcytic Basophilic stippling Poikilocytosis

Macrocytic (MCV > 100 fL) anemia

Megaloblastic macrocytic anemia	Non-megaloblastic macrocytic anemia
• Due to impaired DNA synthesis • **Hypersegmented neutrophils.** (> 5 lobes) • Causes: B12 deficiency and folic acid deficiency anemia	• DNA synthesis is unimpaired • Not associated with hypersegmented neutrophils. • Causes: alcoholism, liver disease, hypothyroidism, reticulocytosis.

B12 (Cobalamin) Deficiency

- Vitamin B-12 binds with intrinsic factor (produced by parietal cells), then absorbed in terminal ileum.
- Causes:
  - Total gastric resection (because intrinsic factor is produced in the gastric fundus)
  - Disorders of the distal ileum (Crohns disease)
  - Intestinal malabsorption syndromes
  - Blind-loop syndrome and broad spectrum antibiotic (bacterial overgrowth depletes B_{12}).

	• Diphyllobothrium latum infestation (freshwater fish)
	• Pernicious anemia:
	  • Type 2 hypersensitivity reaction, autoimmune disease
	  • Damage parietal cells ↓HCl, ↓intrinsic factor, association with other autoimmune diseases
	• Clinical features:
	  • Non-neurologic manifestations
	    • Pallor, angular stomatitis, **Dementia, psychiatric problems, optic atrophy**
	  • Neurologic manifestations
	    • Neurologic symptoms:
	      • Peripheral neuropathy Paresthesia
	      • Subacute combined degeneration of spinal cord characterized by combination of symmetrical posterior column loss (loss of vibration and proprioception), and symmetrical corticospinal tract loss (upper motor neuron signs).
	      • **Classic triad of:** extensors plantars (UMN lesion), absent ankle jerk (LMN lesion), and exaggerated knee jerk.
	      • Pain and temperature sensation may remain intact even in severe cases, as the spinothalamic tracts are preserved.
	• Lab findings:
	  • ↓ Serum B12, ↑ homocysteine, ↑methylmalonic acid, anti-intrinsic factor ab.
	• Abnormal schilling test:
	  • Which is characterized by impaired absorption of vitamin B12 correctable by intrinsic factor
	  • Impaired absorption not corrected by intrinsic factor is characteristic of intestinal malabsorption, such as may occur in Crohn disease, blind-loop syndrome, and giant tapeworm infestation.
	  • Normal absorption is characteristic of vitamin B12 deficiency due to dietary deprivation, which may occur in absolute vegetarians

Folate Deficiency Anemia	• Causes
	  • Malnutrition (e.g., alcoholics)
	  • Malabsorption, drugs (e.g., methotrexate, trimethoprim, phenytoin)
	  • ↑requirement (e.g., hemolytic anemia, pregnancy).
	• Lab findings:
	  • ↑ Homocysteine, normal methylmalonic acid. No neurologic symptoms

Note (Clinical pearls)

- Folate stores are depleted in **3-6 months,** Vit B12 suffiecient for **more than 3 years**
- Folate commonly found in green, leafy vegetables, while **vitamin B12 is found only in foods of animal origin**
- **If someone is deficient in vitamin B12 and folic acid, the vitamin B12 deficiency must be treated first.** Folate and can lead to "steal" of B12 stores causing worsening of neuro complications (SACD)

Normocytic Anemia

- Normocytic, normochromic anemias are classified as nonhemolytic and hemolytic.
- The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic or extrinsic to the RBC) and by the location of the hemolysis (intravascular or extravascular).

Intravascular hemolysis	Extravascular hemolysis
• Characterized by breakdown of RBC'S in the circulation (within the blood vessel) • Findings: • **↓ haptoglobin** • ↑ LDH, schistocytes and ↑ reticulocytes on blood smear. • Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. • Notable causes are mechanical hemolysis (e.g., prosthetic valve), paroxysmal nocturnal hemoglobinuria, and microangiopathic hemolytic anemias.	• Characterized by breakdown of RBC's in reticuloendothelial system i.e. macrophages in spleen, liver and bone marrow • Findings • Macrophages in spleen clear RBCs. • ↑ LDH • No hemoglobinuria/hemosiderinuria • ↑ unconjugated bilirubin, which can cause jaundice

- Note: **Haptoglobin (Hp) binds free Hb. In intravascular hemolysis free HB will be released into circulation, Haptoglobin binds to it (results in ↓) this complex is removed by reticuloendothelial system (mostly spleen)**

Non-hemolytic Normocytic anemia

Aplastic anemia	• Caused by failure or destruction of myeloid stem cells due to: • Radiation and drugs (benzene, chloramphenicol, alkylating agents, antimetabolites) • Viral agents (parvovirus B19, EBV, HIV, HCV) • Fanconi anemia (DNA repair defect) • Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis • Clinical Features • Anemia= weakness, pallor, Neutropenia= Infections, Thrombocytopenia= Bleeding, purpura, and petechiae. • Other abnormalities such as hepatosplenomegaly, lymphadenopathy, or bone tenderness should not be present, and their presence should lead to questioning the diagnosis. • Lab Findings • CBC =pancytopenia • Bone marrow biopsy = most accurate test showing **aplasia or hypoplasia** of marrow cells with fat replacement and decreased cellularity • Treatment: • Withdrawal of offending agent • **Immunosuppressive regimens (e.g., antithymocyte globulin plus cyclosporin)** • Bone marrow allograft • RBC/platelet transfusion • Bone marrow stimulation (e.g., GM-CSF).

Normocytic Anemia (continued)

Intrinsic Hemolytic Normocytic Anemia (E=extravascular, I=intravascular)

Sickle cell disease	• Caused by **point mutation** at position 6 of β-globin chain resulting in substitution of valine for glutamic acid • **Heterozygous condition:** • Also called sickle cell trait i.e. HbAS (60% normal Hb, 40% HbS-sickle Hb) • It produces no anemia • Protective against falciparum malaria (protection is also by G6PD, absence of Duffy blood group antigen)

Sickle cell disease	• **Homozygous condition:**
	  • Also called sickle cell anemia i.e. HbSS (100% HbS, no normal Hb)
	  • It produces anemia
	  • Not protective against falciparum malaria
	• Low O2, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) anemia and vaso-occlusive disease.
	• Chronic leg ulcers
	• Newborns are initially asymptomatic because of ↑ HbF and ↓ HbS.
	• Sickle cells are crescent-shaped RBCs.
	• "Crew cut" on skull x-ray due to marrow expansion from ↑erythropoiesis (also seen in thalassemias).
	• Complications:
	  • Susceptibility to infections
	    • Septicaemia and meningitis →strept pneumoniae
	    • Osteomyelitis → salmonella
	  • Vaso-occlusive crises: (inactivates NO)
	    • Results from microvascular occlusion and causes
	    • Stroke
	    • Mesenteric ischemia
	    • Priapism – painful prolonged erection
	    • Hand-foot syndrome (Dactylitis)→common in infants, painful swelling of hands and feet due to bone infarctions
	    • Acute-chest syndrome →most common cause of death in adults, vaso-occlusion of pulmonary capillaries
	  • **Autosplenectomy →Howell-Jolly bodies**
	• Diagnosis: hemoglobin electrophoresis.
	• Treatment: hydroxyurea (↑ HbF), hydration

Hereditary spherocytosis (E)	• Autosomal dominant
	• Due to defect in membrane protein that makes RBC'S spheroid, vulnerable to splenic sequestration and destruction.
	• Most common mutation:
	  • Ankyrin spectrin (most common),, band-3 and 4
	• Splenomegaly, aplastic crisis (parvovirus B19 infection).
	• Labs:
	  • Peripheral film: spherocytes →small, round RBCs with less surface area and no central pallor
	  • Increased MCHC and Negative coomb's test
	  • Osmotic fragility test: spherocytes rupture in hypotonic salt solution
	• Treatment: Splenectomy

Intrinsic Hemolytic Normocytic Anemia (Continued)

G6PD deficiency (I/E)	• X-linked recessive disorder therefore affects only males
	• Most common form of enzyme deficiency hemolytic anemia
	• **Self-limiting disease**
	• Normal:
	  • G6PD rate limiting enzyme of HMP, normally produces NADPH, which keeps glutathione (GSH) reduced →which protects RBC'S breakdown by breaking hydrogen peroxide
	• Deficiency:
	  • ↓G6PD→↓NADPH→↓GSH→hydrogen peroxide oxidize Hb, which precipitates in the form of **Heinz bodieswhich** →damage RBC's membrane and causes hemolysis
	  • **Heinz bodies** removed from RBC by splenic macrophages →**Bite cells**

	• Anemia is triggered by oxidative stress (fava beans in children, infection, DKA, primaquine) • Labs: • Blood smear shows RBCs with Heinz bodies and bite cells. • **Mnemonic:** "**Stress** makes me eat **bites** of **fava beans** with **Heinz** ketchup."
Pyruvate kinase deficiency (E)	• Autosomal recessive. 2nd most common enzyme defect anemia. • Defect in pyruvate kinase → ↓ ATP → rigid RBCs. • Anemia is chronic and sustained
HbC defect (E)	• Glutamic acid-to-lyCine (lysine) mutation in β-globin.

Paroxysmal nocturnal hemoglobinuria (I)	• ↑ complement-mediated RBC lysis
	• Impaired synthesis of GPI (glycosylphosphatidylinositol) anchors → inactivates complement →protects RBC membrane from complement destruction
	• ↑ Incidence of acute leukemia.
	• Venous thrombosis (most common cause of death)
	• Clinical features:
	  • Associated with aplastic anemia.
	  • Triad: Coombs ⊖ hemolytic anemia, pancytopenia, and venous thrombosis.
	• Lab test:
	  • Flow cytometry demonstrates deficiencies of CD55 and CD59 (CD55/59 ⊖) Most accurate
	  • Sucrose hemolysis test→screening test
	  • Ham's test→confirmatory test
	• Treatment: Eculizumab (inactivates C5 and decreases hemolysis).

Extrinsic Hemolytic Normocytic Anemia

Microangiopathic Anemia	• RBCs are damaged when passing through obstructed or narrowed vessel lumina • Seen in DIC, TTP/HUS, SLE, and malignant hypertension. • Schistocytes ("helmet cells") are seen on blood smear due to mechanical destruction of RBCs
Macroangiopathic Anemia	• Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction. • Schistocytes on peripheral blood smear

Autoimmune Hemolytic Anemia

Warm Antibody Autoimmune Hemolytic Anemia	**Cold Antibody Autoimmune Hemolytic Anemia**
• Mnemonic= (Warm weather is Great, Cold weather is MMMiserable	
• Most common form of autoimmune hemolytic anemia • IgG-mediated, Active at warm temperature (37 degree)	• IgM-mediated, acute anemia triggered by cold

• Causes:
  • Idiopathic (50% cases)
  • May also be seen in association with SLE and CLL and with certain drugs (e.g., α-methyldopa)
	• Causes:
	  • Idiopathic (50% cases)
	  • May also be seen in association with CLL, Mycoplasma pneumonia infections, EBV infections, and infectious Mononucleosis

• Clinical features
  • Can occur in all ages and Both Sexes (but more common in middle-age females).
  • An anemia of rapid onset that may be life threatening.
  • Fatigue. Dyspnea. Jaundice and **Spleenomegaly**	

- **Diagnosis:**
  - Direct Coombs test (aka direct antiglobulin test (DAT)
    - Positive (90% cases)—most important
  - Indirect Coombs test (aka indirect antiglobulin test)
    - May or may not be positive.
  - CBC with peripheral smear
    - Shows spherocytes
- **Management**
  - The underlying cause should be treated (if any known drug it should be avoided) if possible.
  - Steroids (1st line treatment)
  - Splenectomy
    - If prednisone is ineffective or if the disease recurs on tapering the dose
  - Rituximab (2nd line)
  - Immunosuppressive agents
  - High-dose intravenous immune globulin

- **Diagnosis:**
  - Direct Coombs test (aka direct antiglobulin test (DAT)
    - Is positive with complement (C3d) alone
  - CBC with peripheral smear
    - Shows Agglutination (shows only in cold temperature)
  - Elevated Cold Agglutinin Titer
- **Management**
  - The underlying cause should be treated, if possible.
  - Patients should avoid exposure to cold/or keep the patient warm.
  - Steroids, alkylating agents and splenectomy are usually ineffective.
  - Rituximab (1st line treatment--DOC)

Blood Groups

Remember

- General rules:
  - O-negative → universal donor (but can receive only from O –I've)
    - Also remember that O +ive can only receive from O blood group (both +ve & -ve) [
  - AB-positive → universal recipients
  - +ive can only give to +ive
  - –ive can give it to both +ive and –I've
- Note that
  - Anti H antibodies are seen in= Blood group OH

Classification of blood groups (ABO Classification & Rh Classification)

	ABO classification				Rh classification	
RBC type	A	B	AB	O	Rh⊕	Rh⊖
Group antigens on RBC surface	A	B	A&B	None	Rh (D)	None
Antibodies in plasma	Anti-B IgM	Anti-A IgM	None	Anti-A IgM Anti-B IgG	None	Anti-D IgG
Clinical relevance						Treat mother with anti-D IgG during and after each pregnancy to prevent anti-D IgG formation

Blood group	Can donate to	Can receive from
A +ive	• A +ive, AB +ive	• A +ive, A-ive O +ive, O -ive
B +ive	• B +ive, AB +ive+ive	• B +ive, B-ive O +ive, O -ive
AB +ive	• AB +ive	• UNIVERSAL RECIPIENT can receive from anyone whether positive or negative
O -ive	• UNIVERSAL DONOR	• But receive only from O -ive
O +ive	• positive All except O -ive (bcz + cannot give to - and all negatives	• O +ive , O-ive
A -ive	• A +ive, A -ive, AB +ive, AB -ive	• A-ive, O -ive
B -ive	• B +ive, B -ive, AB +ive, AB -ive	• B-ive, O -ive
AB -ive	• AB +ive, AB -ive	• A-ive, B -ive, O -ive, AB -ive

Hemolytic Disease of The Newborn (aka Erythroblastosis Fetalis)

	Rh hemolytic disease of the newborn	ABO hemolytic disease
Interaction.	• Rh ⊖ mother; Rh ⊕ fetus	• Type O mother; type A or B fetus.
Mechanism	• First pregnancy: mother exposed to fetal blood (often during delivery) formation of maternal anti-D IgG. • Subsequent pregnancies: anti-D IgG crosses the placenta → attacks fetal RBCs → hemolysis in the fetus.	• Pre-existing maternal anti-A and/or anti-B IgG antibodies cross placenta → hemolysis in the fetus.
Presentation	• Hydrops fetalis • Jaundice shortly after birth, • Kernicterus	• Mild jaundice in the neonate within 24 hours of birth. • Unlike Rh HDN, can occur in firstborn babies and is usually less severe.
Treatment /Prevention	• Prevent by administration of anti-D IgG to Rh ⊖ pregnant women during third trimester and early postpartum period (if fetus Rh ⊕). • Prevents maternal anti-D IgG production	• Phototherapy or • Exchange transfusion

Splenectomy

- It is best to postpone splenectomy until after childhood, as sudden overwhelming fatal infections, usually due to encapsulated organisms such as pneumococci, may occur.
- Splenectomy should be preceded by appropriate immunization and followed by lifelong penicillin prophylaxis
- Following splenectomy, the spherocytes persist but the Hb usually returns to normal as the red cells are no longer destroyed.

Prophylaxis

- Prophylaxis should be done against infection after splenectomy or splenic dysfunction

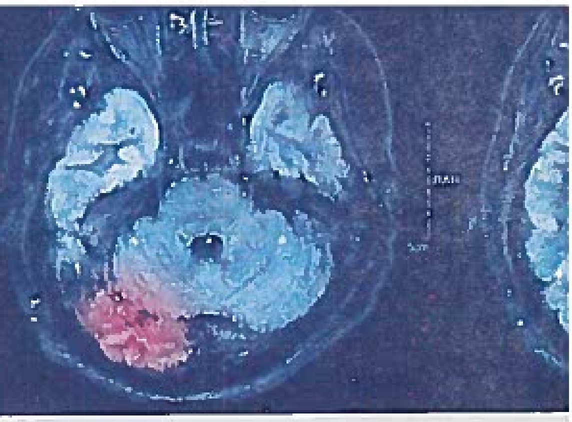
Lifelong Penicillin	• Splenectomy should be preceded by **lifelong penicillin prophylaxis** • Long-term penicillin-V 500 mg 12-hourly (if sensitive, use erythromycin)
Vaccination	• Vaccinate 2-3 weeks before elective splenectomy. • Vaccinate patients undergoing splenectomy against encapsulated organisms especially SHiN • (S pneumoniae >> H Influenzae type B > N meningitidis)

Quick Review

Microcytic (MCV <80 fL)	• Iron deficiency anemia	• Plummer-Vinson syndrome • ↓ Serum iron, ↑ TIBC (↑ only in this anemia), ↓ ferritin (best test).
	• Thalassemia	• β-thalassemia minor→↑HbA2 • β-thalassemia major→↑HbF
	• Anemia of chronic disease	• ↓ Serum iron, ↓ TIBC
	• Lead poisoning	• Basophilic stippling, lead lines, ↓ Heme synthesis
	• Sideroblastic anemia	• ↑ Iron, normal or ↓TIBC, ↑ferritin • Ringed sideroblast
	Megaloblastic macrocytic anemia (Hypersegmented neutrophils)	
	• B12 deficiency anemia	• Hypersegmented neutrophils.(more than five lobes)). • ↓ Serum B12, ↑ homocysteine, ↑methylmalonic acid • Neurological symptoms
	• Folic acid deficiency anemia	• ↑ Homocysteine, normal methylmalonic acid and No Neurological symptoms.
	Non-megaloblastic macrocytic anemia (NO hypersegmented neutrophils)	
	• Alcoholism • Liver disease • Hypothyroidism	• Acanthocyte ("spur cell") in liver disease • No hypersegmented neutrophils.
Normocytic (MCV 80-100 fL)	**Non- hemolytic anemia (reticulocyte count normal or ↓) (MCV >100 fL)**	
	• Aplastic anemia	• ↓ Reticulocyte count, ↑ EPO • Normal cell morphology, but hypocellular bone marrow with fatty infiltration (dry bone marrow tap).
	• Anemia with chronic kidney disease	• ↓Hb, ↑Cr level
	Intrinsic Hemolytic anemia (anemia with intrinsic cause, RC ↑)	
	• Hereditary spherocytosis (membrane defect)	• Spherocytes →small, round RBCs with less surface area and no central pallor • Increased MCHC and Negative coomb's test
	• G6PD	• Most common form of enzyme deficiency hemolytic anemia • Self-limiting disease, Affects only males • Heinz bodies
	• Sickle cell anemia	• Autosplenectomy→Howell-Jolly bodies • Septicaemia and meningitis →strept pneumoniae • Osteomyelitis → salmonella
	• Paroxysmal nocturnal hemoglobinuria	
	Extrinsic Hemolytic anemia (RC ↑)	
	• Autoimmune	• Warm antibody autoimmune hemolytic anemia→ IgG • Cold agglutinin disease: →IgM

	• Microangiopathic • Macroangiopathic • Infections	• Schistocyte ("helmet cell") • Schistocyte ("helmet cell")

Target cell (mnemonic-HALIT) → HbC disease, Asplenia, Liver disease, Iron def. anemia Thalassemia



Chapter 2: Neoplastic, Proliferative and Hemorrhagic Disorders

Leukemias

- Leukemia are malignant disorder of hematopoietic cell compartment, characteristically associated with increased number of white cells in the bone marrow or peripheral blood
- The bone marrow is diffusely infiltrated with leukemic cells, often with encroachment on normal hematopoietic cell development.
- Consequent failure of normal leukocyte (infection), red cell (anemia), and platelet (hemorrhage).
- Infiltration of leukemic cells in the liver, spleen, lymph nodes, and other organs is common.
- **Acute Leukemias:**
    - Failure of cell maturation→***blast cells >20% in bone marrow***
    - Includes:
        - Acute Lymphoblastic Leukemia (**ALL**), Acute Myelogenous Leukemia (**AML**)
- **Chronic leukemia:**
    - Insidious onset of bone marrow failure→***blast cells <20% in bone marrow***
    - Includes:
        - Chronic Lymphocytic Leukemia (**CLL**), Chronic Myelogenous Leukemia (**CML**)

Acute Leukemia

Acute Lymphoblastic Leukemia (ALL)	Acute Myelogenous Leukemia (AML)
• *ALL is the most common malignancy in children.*	• *AML occurs most often in adults.*
• ↑↑Lymphoblast's (B or T-cell lymphocytes)	• A predominance of myeloblasts and early promyelocytes is characteristic.
• Lymphoblasts have agranular cytoplasm (granular in AML)	• *Myeloblasts have granular cytoplasm and stain positive with MPO.*
• Features: ◦ Bone pain and tenderness, lymphadenopathy, spleen and liver enlargement ◦ ***May spread to CNS*** *(cranial neuropathies, vomiting)* ***and testes.*** ◦ *T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome).*	• Features: ◦ ***Auer rods***→fused azurophilic granules in cytoplasm of myeloblasts ◦ Total 8 subtypes; M0 to M8. ◦ *In which M3 AML (called Acute promyelocytic leukemia) carries good prognosis--* ***t(15:17)***
• TdT+ (deoxynucleotidyltransferase) positive in both B and T-CELL • CD10+ (pre-B cells only). • ***t(12;21) better prognosis*** • ***t(9:22) Philadelphia chromosomepoor prognosis.***	• M3 AML: ◦ **Acute promyelocytic leukemia (APML) t(15:17)** ◦ Responds to all-trans retinoic acid (vitamin A) ◦ *DIC is a common presentation*
• *ALL is the form of acute leukemia that is most responsive to therapy*	• AML responds to current therapy more poorly than ALL

• *Associated with Down syndrome*	
• Good prognostic factors ◦ Younger age ◦ WBC <50 × 109/L for B-lineage <100 × 109/L for T-lineage ◦ *Absence of* ***Philadelphia chromosome*** ◦ ***t(12;21) presence***	• Good prognostic factors ◦ **t(15:17)—presence --APML**

Chronic Leukemia

Chronic Lymphocytic Leukemia (CLL) /Small Lymphocytic Lymphoma (SLL)	Chronic Myelogenous Leukemia (CML)	Hairy Cell Leukemia
• *CLL* ***most common overall leukemia****, old age> 60 years* • ↑normal appearing B-lymphocytes that function abnormally. • Most common cause of generalized lymphadenopathy • ***Associated with Autoimmune hemolytic anemia→spherocytes***	• Clonal overproduction of hematopoietic myeloid cell that can differentiate • CML is a disorder of **middle age** (median age -55 years). • Patients usually complain of **fatigue, night sweats, and low-grade fevers** (in absence of any infectious disease)	• Mature B-cell tumor in the elderly.
• **Richter's syndrome:** ◦ Transformation of CLL into more aggressive form, takes the form of diffuse large B-cell lymphoma	• **Blast crisis:** ◦ *Most common cause of death* ◦ *Characterized by transformation to acute leukemia* ◦ *It transform to AML in 70% cases→poor prognosis* ◦ *It transform to ALL in 30% cases→good prognosis*	• B-cell disease in which the leukemic cells exhibit characteristic hair-like filamentous projections
• Lab ◦ CBC peripheral smear ▪ Shows inc wbc count **With lymphocytosis** (criteria for diagnosis >5 × 109/L), Blast cells less than 5% ◦ ***Smudge cells*** (parachute cells): fragile leukemic cells seen in CLL (lab artefact) • Mnemonic CLL = Crushed Little Lymphocytes (smudge cells).	• Lab ◦ CBC peripheral smear ▪ Shows inc wbc count **Basophilia and eosinophilia** may be present Blast cells less than 5% Increased numbers of blasts are suggestive of accelerated phase or blast crisis. ◦ ***↓ LAP (leukocyte alkaline phosphatase)*** ***ABL-BCR required for diagnosis*** Philadelphia chromosome involves fusion of ABL-proto-oncogene on chromosome 9 with break-cluster-region (BCR) on chromosome 22	• Lab • Stains **TRAP** (tartrate-resistant acid phosphatase). Causes marrow fibrosis **dry tap on aspiration.**
• Cytogenetic and immunohistochemistry ◦ Cd5, CD19 and CD20positive **CD10negative**	• Cytogenetics ◦ ***Philadelphia chromose t (9:22) always present (95%).*** ***Absence of Philadelphia chromosomepoor prognosis***	

• SLL same as CLL except CLL has ↑peripheral blood lymphocytosis or bone marrow involvement		
• Treatment: • Mnemonic **FCR**--- **F**ludarabine + **C**yclophosphamide+ **R**ituximab	• Treatment: • TKI's 1st generationImatinib Hydroxyurea	

Lymphoid Neoplasm

Lymphomas

- Lymphomas are neoplasm that arise from lymphoid tissue
- Classified into Hodgkin and Non-Hodgkin lymphoma

Hodgkin Lymphoma	Non-Hodgkin Lymphoma
• ***Localized, single group of nodes, painless, rubbery lymph nodes*** • ***Cervical/supraclavicular** (60-80%), axillary (10-20%), inguinal (6-12%)*	• *Multiple, peripheral nodes, painless lymphadenopathy* • Lymph nodes may be present peripherally or centrally (in the retroperitoneum, mesentery, and pelvis)
• Constitutional ("B") symptoms: fever (>38), sweats, weight loss (>10% over 6 months)	• Constitutional ("B") symptoms: fever (>38), sweats, weight loss (>10% over 6 months) • "B" symptoms less common than in HL
• ***Pel-Ebstein Fever*** (high fever for 1-2 wk., followed by an afebrile period of 1-2 wk.)	• Patients with Burkitt lymphoma are noted to have abdominal pain or abdominal fullness ***Testis and CNS involvement*** *Burkitt's lymphoma, with characteristic jaw lymphadenopathy.*
• Extra-nodal rare.	• Extra-nodal involvement common
• *Contiguous spread* (anatomic spread to adjacent nodes)	• *Non-contiguous spread*
• Bimodal distribution-young adulthood and > 55 years; more common in men except for nodular sclerosing type.	• Peak incidence for certain subtypes at 20-40 years old
• *Strongly associated with EBV.*	• *May be associated with HIV and autoimmune diseases (RA, SLE) & EBV*
• Classification: • Classic HL: • Includes nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte depletion • Non-Classic HL: • Lymphocyte predominance	• Classification: On the basis of Cell type • Neoplasms of Mature B-Cells • Neoplasms of Mature T-Cells

- Staging:
  - Ann-Arbor

Stage-I	Single lymph node
Stage-II	2 or more nodal areas on same side of diaphragm
Stage-III	Involvement of nodes on both sides of diaphragm
Stage-IV	Extra nodal involvement (liver, bone marrow)

- Prognosis is much better than with non-Hodgkin lymphoma.

- Staging:
  - Ann-Arbor

Types of Hodgkin Lymphoma

Nodular Sclerosis	Mixed Cellularity	Lymphocyte Rich	Lymphocyte Depleted	Lymphocyte Predominant
Most common *More common in females*	*2nd Most common* *More common in males*	Common in old males	More common in old males	More common in young males
EBV= negative	*EBV= 70% +ive*	EBV= 30% +ive	EBV= positive	*EBV= negative*
Reed-Sternberg cells + fibrotic bands	Reed-Sternberg cells + NO fibrotic bands	Reed-Sternberg cells + abundant lymphocytes	Reed-Sternberg cells + diffuse fibrosis	*Popcorn cells* i.e. lymphohistiocytic variant of Reed-Sternberg cells
Prognosis= ***Excellent***	*Prognosis=* ***Intermediate***	*Prognosis=* ***Good***	*Prognosis=* ***The Worst***	*Prognosis=* ***The Best***

Types of Non-Hodgkin Lymphoma

Neoplasms of Mature B-Cells

- **Burkitt lymphoma**
  - *t(8;14)* —translocation of c-myc (8) and heavy-chain Ig (14)
    "Starry sky" appearance. *Associated with EBV.*
- **Diffuse large B-cell lymphoma**
  - ***Most** common type of non-Hodgkin lymphoma in adults.*
- **Follicular lymphoma:**
  - *t(14;18)*—translocation of heavy-chain Ig (14) and BCL-2 (18)
  - Presents with painless "waxing and waning" lymphadenopathy.
    Nodular, small cells; cleaved nuclei.
- **Mantle cell lymphoma:**
  - *t(11;14)*—translocation of cyclin D1 (11) and heavy-chain Ig (14)
  - CD5 +ive.

Neoplasms of mature T cells

- **Adult T-cell lymphoma:**
  - *Caused by HTLV (associated with IV drug abuse)*
  - Present with cutaneous lesions, Lytic bone lesions, hypercalcemia
- **Mycosis fungoides/ Sézary syndrome**
  Presents with skin patches/plaques (cutaneous T-cell lymphoma)
  Characterized by atypical CD4+ cells with "cerebriform" nuclei.
  May progress to Sézary syndrome (T-cell leukemia).

Leukemia vs. Lymphoma

- **Leukemia:**
  - Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood.
- **Lymphoma:**
  - Discrete tumor mass arising from lymph nodes. Presentations often blur definitions.
- **Leukemoid reaction:**
  - Acute inflammatory response to infection.
  - ↑WBC count with↑neutrophils and neutrophil precursors such as band cells (left shift).
  - ↑Leukocyte alkaline phosphatase (LAP).

Extra Notes:

- Reed Sternberg cells:
  - *Tumor giant cell seen in Hodgkin disease*
  - *Binucleate or bilobed with the 2 halves as mirror images ("owl eyes").*

Myeloproliferative Disorders

- Results from clonal expansion of multi-potent hematopoietic stem cell
- *JAK-2 gene mutation is often found in chronic myeloproliferative disorders except CML (which has BCR-ABL translocation).*
- It is classified into
  - RBC→Polycythemia Vera
  - WBC→CML
  - Platelets→Essential Thrombocythemia
  - Fibroblasts→Myelofibrosis

Polycythemia Rubra Vera

- Stem cell disorder characterized by elevated RBC mass (erythrocytosis) ± increased white cell and Platelet production
- Diagnosis (WHO criteria) requires
  - Presence of both major criteria and one minor criterion

    "OR"
  - The presence of the first major criterion together with two minor criteria.

Major Criteria	Minor Criteria
1. Haemoglobin >18.5 g/dl in men, 16.5 g/dl in women or other evidence of increased red cell volume 2. Presence of JAK2 mutation	1. Bone marrow biopsy showing hypercellularity for age with trilineage myeloproliferation 2. Serum erythropoietin level below the reference range for normal 3. Endogenous erythroid colony formation in vitro

- **Clinical features:**
  - Marked erythrocytoses and moderate increase in circulating granulocytes and platelets
  - Thrombotic complications such as MI, stroke, PE, DVT due to thrombocytosis (PLT> 400×10^{9}) and hypervisocisty (erythrocytosis)
  - Erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities.
  - ↑Histamine from basophils itching after hot bath, PUD.
  - Gout (Hyperuricemia) due to increased cell turnover
  - **Spleenomegaly**
  - Most Common Symptoms (Mnemonic **PRV**):
    - *Plethora/ Pruritis*
    - *Ringing in ears*
    - *Visual blurriness*

	• *LAP is increased, ↓EPO (only in this type of polycythemia)*
	• *Bone marrow: hypercellular marrow*
	• **Treatment:**
	  ▪ Phlebotomy (Venesection) to keep hematocrit <45%
	  ▪ Hydroxyurea
	  ▪ JAK2 inhibitors (Ruxolitinib)
	  ▪ Allopurinol:
	  ▪ Antihistamines: as needed
	• **Prognosis:**
	  ▪ Median survival if treated is 9-12 y
	  ▪ Transition to myelofibrosis occurs in ~30% or acute leukaemia in ~5%.

Essential Thrombocythemia	• *Increased in platelets with or without increase in WBC and RBC.* • Characterized by clonal proliferation of megakaryotes leading to persistently elevated platelets with abnormal function. • Thrombosis, hemorrhage, microvascular occlusion, erythromelalgia. • *Bone marrow: megakaryocytic hyperplasia*

Primary Myelofibrosis	• Excessive bone marrow fibrosis leading to marrow failure
	Characterized by
	  ▪ Hypermetabolic symptoms: night sweats, fever, weight loss
	  ▪ Anemia, variable WBC's and PLT
	  ▪ Peripheral smear: Leukoerythroblastosis (**tear drop cells**, nucleated RBCs, immature WBCs); large abnormal platelets
	  ▪ Extramedullary hematopoiesis (leading to spleenomegaly).
	  ▪ *BM aspirate→"dry" tap;*
	  ▪ *BM trephine biopsy→severe fibrosis, replacement by reticulin & collagen*
	• JAK2 is mutated in -65% of cases, and MPL is mutated in -40% of cases

Note	• Thrombocytosis:
	  ▪ Primary thrombocytosis refers to essential thrombocythemia
	  ▪ Secondary thrombocytosis also known as reactive thrombocytosis
	  ▪ Cause of secondary thrombocytosis:
	    ▪ Inflammation= RA, IBD
	    ▪ Infection
	    ▪ *Post splenectomy*

Quick Review

Features / Type	Hematocrit	WBCs	Platelets	RBC morphology	Philadelphia Chromosome	JAK2 Mutations	Bone Marrow
Polycythemia Rubra Vera	↑	↑/N	↑/N	N	⊖	⊕	Hypercellular
Essential Thrombocythemia	Normal	↑/N	↑↑	N	⊖	⊕	Megakaryocytic hyperplasia
Primary Myelofibrosis	↓	Variable (N/↑/↓)	Variable	Abnormal	⊖	⊕	Dry tap
CML	Normal	↑↑	↑/N	N	⊕	⊖	Hypercellular

Extra notes

Secondary Polycythemia	• Causes: · Hypoxia cardiac disease, pulmonary disease, high altitude · Carboxyhemoglobin: smoking · Kidney lesions · Erythropoietin-secreting tumors (rare) · Abnormal hemoglobin's (rare) · Diuretics use • A secondary cause of polycythemia should be suspected if splenomegaly is absent and the high hematocrit is not accompanied by increases in other cell lines. Treat underlying cause · O2 for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumors
Relative' or 'apparent' Polycythaemia (Gaisböck's syndrome)	• Stress-induced, burns or dehydration • The red cell volume is normal, but as the result of a decreased plasma volume, there is a relative Polycythaemia. • More common than PV and occurs in middle-aged men, particularly in smokers who are obese and hypertensive. • Treatment:

Myelodysplastic Syndromes

- Heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias, and a variable risk of **transformation to acute Leukemias**
- **Diagnosed by**
  - Pancytopenia with abnormal shapes of RBC's (macro-ovalocytes, sideroblasts), WBC's (bi-lobed or unsegmented nuclei), PLT (giant hypogranular platelets)
  - Bone marrow (definitive diagnosis)→***dysplastic and often normocellular/hypercellular***
- **Management:**
  - Patients with <5% blasts in the bone marrow
    - Managed conservatively with red cell and platelet transfusions and antibiotics for infections, as they are needed.
    - Haemopoietic growth factors (e.g. erythropoietin, G-CSF) may be useful in some patients.
  - Patients with >5% blasts have a less favorable prognosis.
    - Supportive care
    - Stem cell transplantation if age <65 yr.
    - Epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-azacytidine), histone deacetylase inhibitors

Clinical pearls:

- Repeated phlebotomy intentionally produces iron deficiency, the requirement for phlebotomy should gradually decrease. (It is important to avoid medicinal iron supplementation)
- MDS Vs. Aplastic Anemia
  - Both causes pancytopenia
  - Aplastic anemia shows Hypocellular bone marrow while MDS shows normocellular or hypercellular

MDS Vs. Myeloproliferative disorders

Myeloproliferative disorders	MDS
Cells mature normally, but they have an abnormally high amount of proliferation—hence the name proliferative	*Cells mature abnormally described as dysplastic (hence, Myelodysplastic syndromes)*
This leads to high numbers of cells in the blood	These dysplastic cells are often so odd and non-functional that they die. This results in lower numbers in the blood

Chromosomal translocation

Translocation	Associated disorder
t(8;14)	*Burkitt lymphoma (c-myc activation)*
t(9;22) (Philadelphia chromosome)	*CML (BCR-ABL hybrid)*
t(11;14)	*Mantle cell lymphoma (cyclin D1 activation)*
t(14;18)	*Follicular lymphoma (BCL-2 activation)*
t(15;17)	*M3 type of AML*

Plasma Cell Disorders

Paraproteinemias

- Gammopathy refers to over production of one or more classes of immunoglobins
- Polyclonal gammopathy means that a single clone of plasma cells produce different immunoglobins (Ig)
- Monoclonal gammopathy means that a single clone of plasma cells produce identical immunoglobins (Ig)
- **Monoclonal immunoglobins are called M-proteins or Paraproteins**

Multiple Myeloma	Monoclonal Gammopathy Of Uncertain Significance	Waldenstrom's Macroglobulinemia

• Plasma cell neoplasm (plasma cell are formed by B-cells)
• In Multiple Myeloma plasma cells are monoclonal which show M-Spike on protein electrophoresis
• Fried egg appearance on histology
• Most common type of monoclonal Ig →IgG (55%), IgA (25%)
• Associated with:
  ◦ Susceptibility to infection (due to reduction in the normal immunoglobulin levels)
  ◦ Severe bone pain (most commonly backache)
  ◦ *Primary amyloidosis* (AL)
  ◦ *M spike on serum protein electrophoresis*
  ◦ Bone marrow: Russell bodies (intracytoplasmic inclusions), Dutcher bodies (intanuclear inclusions)
• **Clinical features:** (Think **CRAB**)
  ◦ *HyperCalcemia*
  ◦ *Renal injury* (due to Ig light chains in *urine--Bence Jones protein*, and due to hypercalcemia)
  ◦ *Anemia* (bone marrow infiltration with plasma cells)
  ◦ *Bone lytic lesions/Back pain* (spinal cord compression & lytic lesions usually seen in the spine, skull, long
	• *Most common monoclonal gammopathy*
	• *Characterized by small IgG M-spike*
	• *Increased risk of conversion to MM*
	• No urinary BJ protein
		• Also known as Lymphoplasmacytic Lymphoma
		B-cell neoplasm that secrete monoclonal IgM
		IgM M-spike
		Hypervisocisty syndrome (e.g., ***blurred vision, Raynaud phenomenon)***
		Investigations and Diagnosis
		  ◦ Bone marrow shows plasmacytoid lymphocytes
		  ◦ Bone lesions usually not present
		  ◦ Blood work rarely see hypercalcemia
		• *Waldenstrom's macroglobulinemia accounts for* ***85% of all cases of hyperviscosity syndrome***
		• Treatment: plasmapheresis

bones and ribs.)

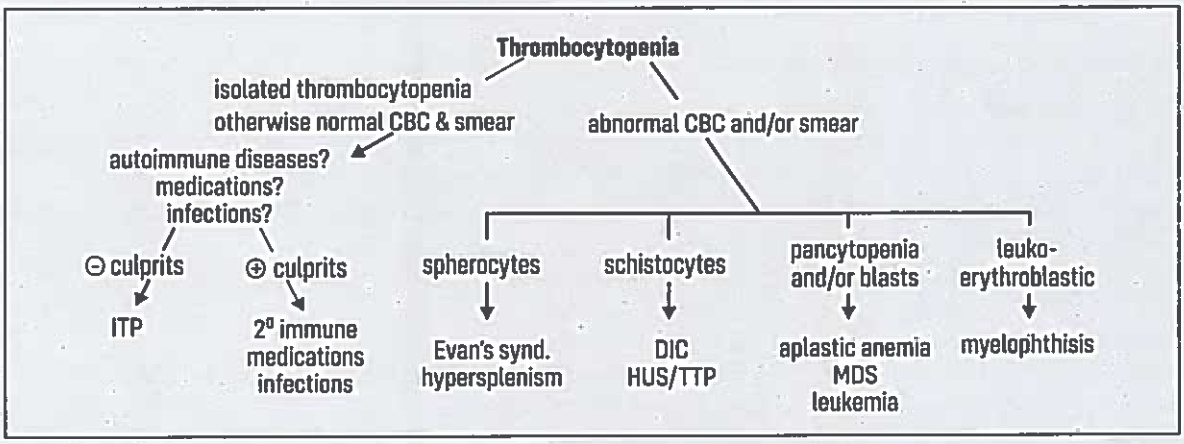
- Neurologic: cord compression; **POEMS** (**P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M** protein, **S**kin changes) syndrome

- Prognosis:
  - *oβ2-microglobulin and LDH levels reflect tumor burden*
    Worse prognosis: Del. Of chromosome 17p13

Platelet Disorders (Thrombocytopenia)

- Dominant features include petechial cutaneous bleeding, intracranial bleeding, and oozing from mucosal surfaces.
- Characteristics include↓***platelet count and↑bleeding time.***

Approach to thrombocytopenia



Immune Thrombocytopenia (ITP)

- ITP is an autoimmune condition
- ITP is mediated by autoantibodies, *most often directed against the platelet membrane glycoprotein IIb/IIIa,*

	Childhood ITP	Adult ITP
Peak Age	• 2-6 yr.	• 2-6 yr.
Gender	• None	• F>M (3:1)
History	• Recent viral infection, including varicella zoster or measles	• Mostly idiopathic, although it can be associated with ◦ Connective tissue disease (such as SLE), ◦ Lymphoproliferative disease (such as lymphoma), ◦ Medications ◦ Infections (such as hepatitis C virus and HIV infections) ▪ HCV--- cirrhosis-related splenomegaly ▪ HIV--- direct suppression of platelet ▪ production
Spontaneous Remissions	• 80% or more	• Uncommon

- **Terminology of ITP**
  - Primary: isolated thrombocytopenia (platelet count <100x109/L) with no other cause of thrombocytopenia
  - Secondary: thrombocytopenia associated with another condition (e.g. HIV, HCV, SLE, CLL)
  - Drug-induced: drug-dependent platelet antibodies causing platelet destruction
    - Mnemonic: **HANDER**

      Heparin, Acetaminophen, Amiodarone, Amphotericin B, H2-Antagonists, NSAIDs , Ethambutol, Rifampicin
- **Clinical Presentation**
  - Easy bruising, purpura, epistaxis and menorrhagia are common when PLT < 20,000 -30,000
  - Physical examination is normal except for evidence of bleeding.
  - ***Splenomegaly is rare.***
- **Investigations**
  - CBC---- isolated ↓PLT (100,000/ L); (10% have ITP + AIHA called**Evans syndrome)**
  - PT and aPTT: normal
  - Peripheral blood film: decreased platelets, giant platelets (rule out platelet clumping)
- **Treatment**
  - Steroids, IVIG, splenectomy (for refractory ITP).

Other Diseases of Platelets

Gestational Thrombocy topenia	• Gestational thrombocytopenia **(platelet counts no lower than 70 × 10^9/L)** is a benign, mild thrombocytopenia associated with mostly 3rd trimester of pregnancy. • Outcome/Prognosis • Gestational thrombocytopenia and thrombocytopenia associated with preeclampsia and eclampsia usually resolves promptly after delivery.
Bernard-Soulier syndrome	• *Autosomal recessive disorder characterized by unusually large platelets and by **lack of a platelet-surface glycoprotein (Gplb)** needed for platelet adhesion.* • As a result defect in platelet-to-vWF adhesion. • Diagnosis: • *CBC (peripheral smear)----low PLT and giant platelets* • *Bleeding time---prolonged* • *Platelet flow cytometry –confirms the diagnosis* • *Management:* ◦ Supportive (Avoid anti-platelet agents, Anti-fibrinolytic agents--- Tranexamic acid, Platelet transfusion, Desmopressin and factor VIIa)

Glanzmann thrombas thenia	• Inaggregability of platelets due to **hereditary deficiency of platelet-surface GpIIb-IIIa** required for formation of fibrinogen bridges between adjacent platelets
	• As result there is failure of platelet to platelet aggregation
	• Diagnosis:
	  ◦ *CBC (peripheral smear)----**Normal PLT's***
	  ◦ ***Bleeding time---prolonged***
	  ◦ **Platelet flow cytometry –confirms the diagnosis**
	• Management:
	  ◦ Supportive (Avoid anti-platelet agents, Anti-fibrinolytic agents--- Tranexamic acid, Platelet transfusion, Desmopressin and factor VIIa)

Von Willebrand Disease	• *Autosomal dominant, (type 3 is autosomal recessive)* ***Most common inherited bleeding disorder*** ↓WF→defect in platelet-to-vWF adhesion→Defect in platelet plug formation *Intrinsic pathway coagulation defect↑PTT (vWF acts to carry/protect factor VIII).* Labs:

	• ↑bleeding time, ↑PTT • **VWF: Antigen** (determine how much VWF is present). • **VWF: Ristocetin** cofactor activity (determine how well VWF bind to platelet). • **Factor VIII (determine how well VWF chaperon with FVIII)--Decreased,** • Treatment: • **Desmopressin,** which releases vWF stored in endothelium. • **vWF- product (containing factor VIII)** • Antifibrinolytic agents • *Pregnant patients with vWD usually do not require treatment at the time of delivery because of the natural physiologic increase in vWF levels.*
Disseminated intravascular coagulation (DIC)	• Widespread activation of clotting leading to deficiency in clotting factors bleeding state. Causes: (Mnemonic: **STOP Making New Thrombi**). • **S**epsis (gram ⊖), **T**rauma, **O**bstetric complications, acute **P**ancreatitis, **M**alignancy, **N**ephrotic syndrome, **T**ransfusion • Labs: • Schistocytes, ↑*fibrin degradation products* ***(d-dimers)***, ↓*fibrinogen*, ↓*factors V and VIII*, ***↑BT, ↑PT, ↑aPTT***

Platelet Disorders (continued)

Thrombotic thrombocytopenic purpura (TTP) & Hemolytic-uremic Syndrome (HUS)

	Thrombotic thrombocytopenic purpura (TTP)	Hemolytic-uremic syndrome (HUS)
Definition	Vascular occlusive disorders w/ systemic (TTP) or intrarenal (HUS) PLT aggregates leading to thrombocytopenia & mechanical injury to RBC's	
Epidemiology	• Predominantly adult	• Predominantly children and elderly
Etiology	• *Deficiency of von Willebrand factor (vWF) metalloprotease (ADAMTS 13).* • Insufficient ADAMTS-13 activity allows vWF multimers to accumulate in microcirculation which leads to platelet aggregation/thrombocy topenia and hemolysis of RBCs	• *Shiga toxin* ***(E. coli serotype 0157:H7, Shigella dysentry) in 90%*** Some cases: heritable deficiency in function of complement regulatory proteins
Clinical Features	• TTP ----**PENTAD** • *Thrombocytopenia* • *MAHA (microangipathic hemolytic anemia)* • *Neurological symptoms: headache, confusion, focal defects, seizures* • *Renal failure* • *Fever*	• HUS---- **TRIAD** • *Thrombocytopenia* *MAHA* *Renal failure* ***(more marked in HUS)***
Investigations (both TTP & HUS)	• CBC and blood film ----decreased platelets and schistocytes • **PT, aPTT, fibrinogen ---- normal** • Markers of hemolysis----increased unconjugated bilirubin, increased LDH, decreased haptoglobin • **Negative Coombs test** • Creatinine, urea, to follow renal function • Specific for HUS • Stool culture OR Stool assays for E coli • Specific for TTP • Reductions in ADAMTS-13 activity	

Treatment	• Medical emergency
	• **Plasma exchange ± steroids (is the mainstay of the treatment)**
	• **Platelet transfusion avoided** unless life-threatening bleed (because associated with Inc. risk of microvascular thrombosis)
	• Cryoprecipitate and FFP (fresh frozen plasma) both contain ADAMTS-13.and transfused it if plasmapheresis is not immediately available
	• TTP mortality ~90% if untreated
	• Disease activity & relapse is monitored by measuring the platelet count and serum LDH.
	• TTP relapse following initial treatment,
	  ◦ Plasma exchange should be reinstituted.
	  ◦ If ineffective, second-line treatments includes
	    ▪ **Rituximab** corticosteroids, IVIG, vincristine, cyclophosphamide, and splenectomy.
		• Supportive therapy (fluids, RBC transfusion, nutrition, etc.)
		• Some evidence for plasma exchange
		• Dialysis
		• **Eculizumab**
		• is a humanized monoclonal antibody that binds to complement protein C5, blocking its cleavage into C5a and the cytotoxic membrane attack complex C5b-9, thus inhibiting complement activation
		• Neisseria meningitides vaccination must be performed before starting Eculizumab.

Coagulation disorders

Prothrombin time PT • Mnemonic: WEPT 1972	• PT used to check extrinsic and common pathway, which is a measure of factors II, V, VII, X, and fibrinogen→↑PT • Factors X, IX, VII, and II, protein C and S are Vitamin K dependent factors • *Warfarin acts on extrinsic pathway* (inhibit the enzyme Vit-k reductase) • *INR (international normalized ratio) — Most common test used to follow patients on warfarin* • *Warfarin acts on Extrinsic pathway, **PT** is used to check it, factors are **10, 9 ,7, 2***
PTT/ APTT • Mnemonic: PT Trainer made us did HIP exercises while counting from **8- two- 12.**	• PTT is used to check common and intrinsic pathway, which is a measure of factors II, V, VIII, IX, X, XI, XII, and fibrinogen, defect→↑PTT Heparin acts on intrinsic pathway PTT is used to check Intrinsic Pathway, factors are 8, 9, 10, 11, 12 and 2

- Coagulation disorders can be due to clotting factor deficiencies or acquired inhibitors.

Disorder	PT	APTT	Mechanism and Comments
Haemophilia	—	↑	• Intrinsic pathway coagulation defect. • **Hemophilia A:** deficiency of factor VIII→↑PTT; X-linked recessive. • **Hemophilia B:** deficiency of factor IX→↑PTT; X-linked recessive. • **Hemophilia C:** deficiency of factor XI→↑ PTT; autosomal recessive. • Characteristics include bleeding into muscles, subcutaneous tissues, and *joints (hemarthroses).* • *The disorder is associated with prolongation of the APTT (or PTT) and a normal bleeding time, platelet count, PT, and thrombin time.* • *Treatment: desmopressin + factor VIII concentrate (A); factor IX concentrate (B); factor XI concentrate (C).*
Vitamin K deficiency	↑	↑	• In adults, vitamin K deficiency is most often caused by fat malabsorption from pancreatic or small-bowel disease In neonates, vitamin K deficiency causes hemorrhagic disease of the newborn, which is due to deficient exogenous vitamin K in breast milk in association with incomplete intestinal colonization by vitamin K-synthesizing bacteria. *(Neonates lack enteric bacteria, which produce vitamin K)* *Results include decreased activity of clotting factors II, VII, IX, and X and are reflected by prolongation of the PT and APTT.*

Heparin-Induced Thrombocytopenia

	Heparin-Induced Thrombocytopenia type I	Heparin-Induced Thrombocytopenia type II
Mechanism	• Non immune • Direct heparin mediated platelet • aggregation	• Immune mediated • Ab recognizes a complex of heparin and platelet factor 4 (PF4) leading to platelet activation via platelet Fc receptor and activation of coagulation system
Onset	• After 1–4 days	• After 5–15 days; but can occur in 24 h if prior of heparin therapy exposure w/in 100 d (persistent Ab).
Platelet nadir	• > 100,000/µL	• <60,000/µL, PLT fall more than 50%
Sequelae	• None	• Thrombotic events (HITT) in 30–50%
Management	• Can continue heparin & observe	• Discontinue heparin Alternative anticoagulation

Thrombotic Disorders

Diseases	Description
Factor V Leiden	• *This is the most frequent cause of hereditary thrombophilia* (hereditary thrombophilia is prothrombotic familial syndrome occurring most often in adolescents or young women) • This is an abnormal factor V protein with a specific mutation that alters the cleavage site targeted by APC. • *The mutation prevents the cleavage and inactivation of the mutant factor Va by APC, a phenomenon referred to as **"hereditary resistance to activated protein C"**.*
Antiphospholipid antibody syndrome	• This prothrombotic disorder is characterized by autoantibodies directed against a number of protein antigens complexed to phospholipids. • *1° or 2° autoimmune disorder (**most commonly in SLE**).* • *Diagnose based on clinical criteria including history of thrombosis (arterial or venous) or **spontaneous abortion** along with laboratory findings* • *Lab findings: lupus anticoagulant (↑aPTT), anticardiolipin antibody, anti-β2 glycoprotein antibodies.* • Treat with systemic anticoagulation. Rememeber: Anticardiolipin antibody, can cause a falsepositive serologic test for syphilis
Protein C or S deficiency	• ↓Ability to inactivate factors Va and VIIIa. • ↑Risk of thrombotic skin necrosis with haemorrhage after administration of warfarin. If this occurs, think protein C deficiency.

Quick summary

Disorder	PT	aPTT	Platelet count	Bleeding time	Notes
Heparin	↑	↑↑	Normal	Normal	
Liver Disease	↑	↑	↓/Normal	↑/Normal	↑AST
Vit K def	↑↑	↑	Normal	Normal	
Haemophillia	Normal	↑↑	Normal	Normal	
vWD	Normal	↑↑	Normal	↑	
HUS	Normal	Normal	↓	↑	Stool culture for E.coli
TTP	Normal	Normal	↓	↑	Reduction in ADAMTS-13 activity
DIC	↑	↑	↓	↑	↑D-dimers

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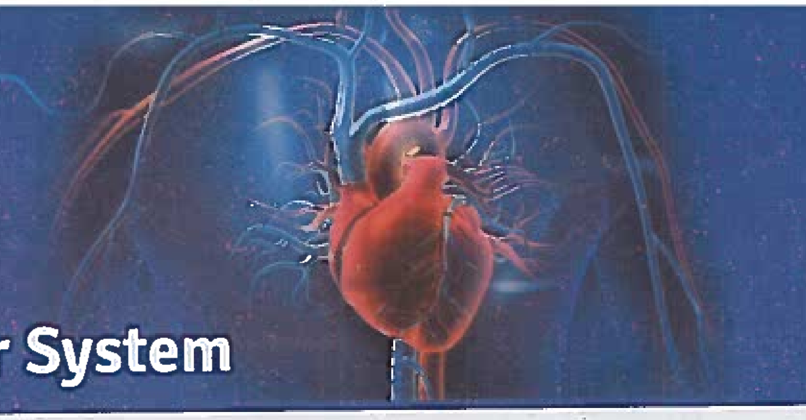


Chapter 3: Cardiovascular System

Arterial Disorders

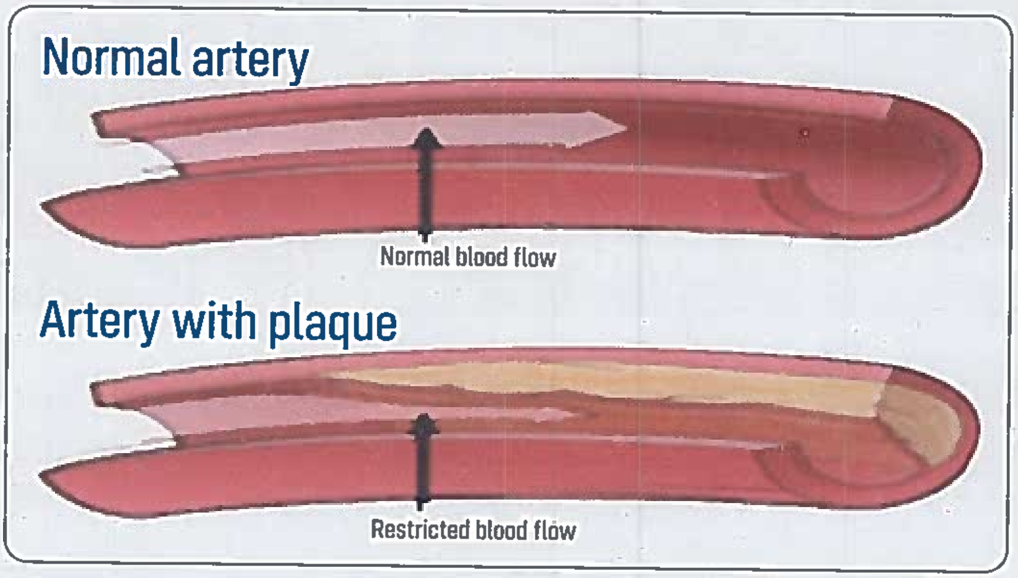
Arteriosclerosis
(Literally means hardening of arteries, 3 patterns)

1. **Monckberg medial calcific sclerosis**
   - Dystrophic calcification of muscular arteries in persons older than age 50
   - Involves media (so as intima not involved obstruction do not occur).
   - Ring like calcification seen in media (characteristic), pipestem appearance on x-ray
   - Example: radial and ulnar arteries

2. **Arteriosclerosis:** Hardening of small arteries and arterioles

Hyaline arteriosclerosis	Hyperplastic arteriosclerosis
Due to Inc deposition of proteins	*Due to smooth muscle hyperplasia*
In kidneys benign nephrosclerosis	*In kidneys malignant nephrosclerosis*
Associated with DM and essential hypertension	Associated with malignant hypertension
	It may be accompanied by necrotizing arteriolitis
	Concentrated, laminated, onion skin appearance

3. **Atherosclerosis**
   - Refers to lipid deposition and intimal thickening (so causes obstruction) of large and medium sized arteries
   - Resulting in fatty streaks and atheromatous plaques
   - Risk factors
     - Modifiable
       - Smoking, hypertension, hyperlipidemia (↑LDL and ↓HDL), diabetes.
       - Obesity, physical inactivity, stress (type-A personality). Chlamydia pneumonia infection,
     - Nonmodifiable:
       - Age, sex (Increase in men and postmenopausal women), family history.
   - Common sites
     - *Abdominal aorta > coronary artery > popliteal artery > carotid artery > circle of Willis*
   - Complications:
     - Rupture, ulceration, haemorrhage
       Thrombus, embolism

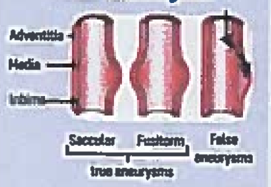


Arterial Disorders (continued)

Aneurysm

- Localized abnormal dilation of blood vessel.

True Aneurysm

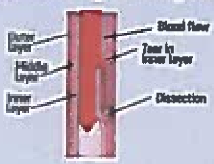


- Involves all three layers or attenuated wall of heart
- Examples: atherosclerotic aneurysm, syphilitic aneurysm, left ventricular aneurysm
- Types:
  - Saccular aneurysm:
    - Spherical outpouching (involving only a portion)
  - Fusiform aneurysm:
    - Circumferential dilation

False Aneurysm

- Breach in vascular wall, leading to an extravascular hematoma (pulsating hematoma)

Dissecting Aneurysm



- Arises when blood enters wall of an artery dissecting between its layers
  Example: aortic dissection:
  - *Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (e.g., Marfan syndrome).*
  - *Can present with **tearing chest pain**, of sudden onset, radiating to the back +/− markedly **unequal BP in arms.***
  - CXR shows mediastinal widening.
  - Can result in rupture, pericardial tamponade, death.
  - Two types:
    - Stanford type A (proximal): involves ascending aorta. May extend to aortic arch or descending aorta. Treatment is surgery.
    - Stanford type B (distal): involves descending aorta and/or aortic arch. No ascending aorta involvement. Treat medically with β-blockers, then vasodilators

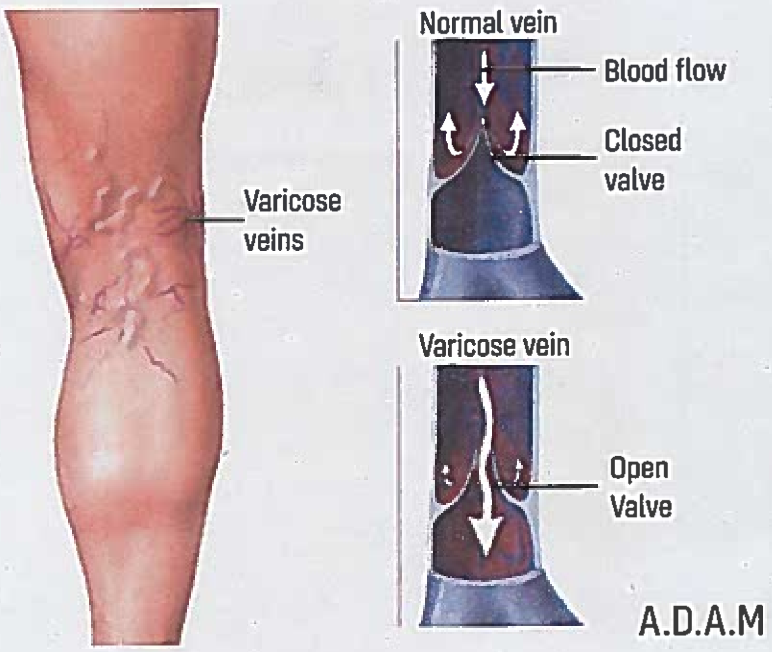
Berry Aneurysms

- *Are small, saccular lesions most often seen in the smaller arteries of the brain, especially in the **circle of Willis***
- They are unrelated to atherosclerosis.
- Berry aneurysms are not present at birth but develop at sites of congenital medial weakness at bifurcations of cerebral arteries.
- These aneurysms are *the most frequent cause of **subarachnoid haemorrhage.***
- *Often, there is an association with **adult polycystic kidney disease***

Abdominal Aortic Aneurysm	• *Atherosclerotic aneurysms most frequently occur in the descending, especially the abdominal aorta.* • *Associated with atherosclerosis.* • Risk factors include history of tobacco use, ↑ age, male sex, family history. • *May present as palpable pulsatile abdominal mass*
Syphilitic (Luetic) Aneurysm	• *Manifestation of tertiary syphilis.* • Characterized by obliterative endarteritis of the vasa vasorum and necrosis of the media, "Tree bark appearance" • *Unlike atherosclerotic aneurysms, syphilitic aneurysms characteristically involve the ascending aorta.* • *Clinical findings: Aortic valve regurgitation and Brassy cough (due to compression of left recurrent laryngeal nerve)*

Venous Disorders

Varicose Veins	• Abnormally dilated, torturous vein. Causes: ◦ Prolonged standing ◦ Pregnancy ◦ Aging ◦ Obesity • Common sites: ◦ Superficial saphenous vein (most common) ◦ Anorectal region: haemorrhoids ◦ Left scrotal region: varicocele
Thrombophlebitis and Phleothrombosis	• Thrombophlebitis refers to venous thrombosis due to inflammation or infection. • Phleothrombosis refers to venous thrombosis without inflammation or infection • Predisposing factors include venous circulatory stasis or partially obstructed venous return, such as occurs with cardiac failure, pregnancy, prolonged bed rest, or varicose veins.



Raynaud's disease and Raynaud's phenomenon

Raynaud's disease	Raynaud's phenomenon
Medium sized vessel vascultitis involving digital vessels in fingers and toes	Medium sized vessel vascultitis involving digital vessels in fingers and toes
Caused by: • *Episodic vasospasm resulting from exaggerated vasomotor response to cold or stress*	Caused by: • *SLE* *Systemic sclerosis* *Atherosclerosis* *Buerger disease*

Vascular Tumors

Benign Tumors

Spider telangiectasia	• Dilated subcutaneous arteries • *Associated with hyperestrinism, as seen in chronic liver disease or pregnancy.*
Hereditary hemorrhagic telangiectasia (Osler-Weber-rendu syndrome)	• *Is an autosomal dominant condition.* • Characterized by localized dilation and convolution of venules and capillaries of the skin and mucous membranes. • It is often complicated by epistaxis or gastrointestinal bleeding.
Hemangioma (angioma)	• Malformation of a larger vessel. It is the most common tumor of infancy *Responsible for port-wine stain birthmarks.* It includes the following types: • Cavernous hemangioma (large and less well circumscribed, involves deep structure). • Capillary hemangioma (small and well circumscribed, involves superficial structures)
Glomangioma (glomus tumor)	• Small, purplish, painful subungual nodule in a finger or toe. Painful, red-blue tumor under fingernails

Port Wine stain birthmarks

Malignant tumors

Angiosarcoma	• Malignant endothelial tumor • It is associated with toxic exposures to arsenic or the radioactive diagnostic agent thorium dioxide (thorotrast). • *Polyvinyl chloride is specifically associated with angiosarcoma of the liver.* • It may arise in the skin of the breast following radiation therapy for breast cancer.
Kaposi sarcoma	• Is a malignant vascular tumor • *Associated human herpes virus 8 (HHV-8), also called Kaposi sarcoma herpes virus (KSHV).* • *Epidemic KS occurs as a component of acquired immunodeficiency syndrome (AIDS)*

Vasculitis

- Can be infectious and non-infectious (immune mediated).

Large vessel vascultitis

(involves aorta and larger branches to extremities)

Giant Cell (Temporal) Arteritis	• Most common • Granulomatous inflammation • *Common sites: temporal, ophthalmic artery* • *Clinical findings: throbbing headache (Unilateral), jaw claudication. May lead to irreversible blindness due to ophthalmic artery occlusion.* • *Associated with polymyalgia rheumatica.* • Diagnosis: temporal artery biopsy
Takayasu Arteritis	• *Pulse less disease (weak upper extremity pulses)* Granulomatous thickening and narrowing of aortic arch and proximal great vessels

Medium sized vascultitis

(involves main visceral arteries and their branches)

Polyarteritis Nodosa	• Typically involves renal and visceral vessels, *sparing pulmonary arteries.* • ***Hepatitis B seropositivity in 30% of patients***
Kawasaki Disease (also called Mucocutaneous lymph node syndrome	• *Self-limiting disease* Affects mostly Asian children < 4 years old. Mnemonic: **CRASH** Conjunctival hemorrhagic edema, Rash (polymorphous→desquamating), Adenopathy (cervical), Strawberry tongue (oral mucositis), Handfoot changes (edema, erythema) • *May develop coronary artery aneurysms, thrombosis or rupture can cause death*
Buerger Disease (Thromboangiitis Obliterans)	• *Heavy smokers, males < 40 years old.* • Intermittent claudication may lead to gangrene. • *Autoamputation of digits* • *Raynaud phenomenon is often present*
Small Sized Vascultitis	
ANCA Positive	• *C-ANCA positive→Wegner Granulomatosis* *P-ANCA positive→Churg Strauss Syndrome and Microscopic Polyangiitis*
ANCA Negative (HSP)	• *Henoch Scholenin Puprura*

Wegener Granulomatosis	• Focal necrotizing vasculitis. *Necrotizing granulomas in the lung and upper airway* Necrotizing glomerulonephritis
Microscopic Polyangiitis	• No granulomas
Churg- Strauss Syndrome (PAVE)	• **P**-ANCA positive, **A**sthma + **V**asculitis + **E**osinophilia
Henoch-Schönlein Purpura	• Most common childhood systemic vasculitis. Often follows URI. Classic Triad: · *Skin: palpable purpura on buttocks/legs* · *Arthralgias* · *GI: abdominal pain* • *Associated with IgA nephropathy (Berger disease)*

Hypertension

Essential Hypertension	• Hypertension of unknown Etiology (most common). • Causes: · Genetic factors Environmental factors: like Dietary sodium intake, stress, obesity, cigarette smoking, and physical inactivity
Secondary Hypertension	see table below

Renal disease (most common)	Endocrine	Cardiovascular	Neurologic
• Renal artery stenosis • Renin producing tumors • Polycystic disease • Chronic renal disease	• Primary aldosteronism (Conn syndrome) • Pheochromocy toma • Pregnancy induced • Adrenocortical hyper function	• Coarctation of aorta • Polyarteritis nodosa • Rigidity of aorta	• Stress • Sleep apnea • Psychogenic

Malignant Hypertension

• Characteristic features include a marked increase in diastolic blood pressure (more than 120)
Focal retinal hemorrhages and papilledema, left ventricular hypertrophy, and left ventricular failure.
It produces the renal changes resulting in *"flea-bitten"* kidney, multiple pinpoint petechial hemorrhages on the kidney surface

Hypertension Urgency	Hypertension Emergency
• Severely elevated BP (ie, systolic BP >220 mm Hg or diastolic BP >120 mm Hg) with **no evidence of target organ damage**	• A condition in which elevated BP results in **target organ damage.** · **Accelerated HTN:** typically defined as an SBP >210 mm Hg and DBP >130 mm Hg presenting with headaches or focal neurologic symptoms · **Malignant HTN:** which requires the presence of papilledema
• Needs BP reduction in several hours	• Hypertensive emergencies **require immediate BP reduction** by 20% to 25% to prevent or minimize end-organ damage

Angina

- Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no myocytes necrosis.
- Pain due to angina is less than 30 minutes and more than 30 minutes in MI

Stable Angina	• Usually, 2° to atherosclerosis pain that is precipitated by exertion usually with ST depression on ECG Relieved with rest or nitroglycerin
Variant (Prinzmetal) Angina	• Occurs at rest 2° to coronary artery spasm. intermittent chest pain at rest Transient ST Elevation on ECG. Treat with Ca2+ channel blockers, nitrates, and smoking cessation (if applicable).

Acute Coronary Syndrome

(Term used to describe unstable angina, NSTEMI and STEMI)

Unstable Angina	NSTEMI (Subendothelial Infarct)	STEMI (Transmural Infarct)
• Rapidly worsening angina (crescendo angina)	• Myocardial necrosis (coagulative) limited to the interior one-third of the wall of the left ventricle.	• Myocardial necrosis (coagulative) entire ventricular wall from the endocardium to the epicardium.
• *Negative cardiac enzymes*	• *Elevated cardiac enzymes*	• *Elevated cardiac enzymes*
• *ST depression with/ without T-wave inversion*	• *ST depression with/without T-wave inversion*	• *ST segment elevation*

Complications

Time	Complication
0-3 days	• Cardiac arrhythmia · *Arrhythmia is the most common cause of death in the first several hours following infarction.* · *Most common complication of MI* · *Ventricular fibrillation is the leading cause of sudden death in acute MI* · CHF & Cardiogenic shock
3-7 days	• Myocardial rupture · Cardiac tamponade (Becks triad) ▪ Hypotension ▪ Dilated neck veins. ▪ Muffled heart sounds. · Acute MR · Post infarction fibrinous pericarditis
4-8 weeks	• Ventricular aneurysm/ pseudoaneurysm Dressler's syndrome · *Autoimmune fibrinous pericarditis* *Characterised by pleuritic pain and fever.*

Type of MI and localization on ECG

- *Commonly Occluded Coronary Arteries, LAD > RCA > circumflex*

I Lateral	aVR	V1 Septal	V4 Anterior
II Inferior	aVL Lateral	V2 Septal	V5 Lateral
III Inferior	aVF Inferior	V3 Anterior	V6 Lateral

Cardiac Enzymes and Diagnosis

- In first 6 hours ECG is gold standard
- Most specific=Troponin I > Trop T
- Most sensitive =Myoglobin
- CK-MBUseful in diagnosing reinfarction following acute MI, because levels return to normal after 48 hours

	CK-MB	Troponin I	LDH	Myoglobin
4 hours		Weakly positive		
6 Hours	Weakly positive	Weakly positive		Peaks
12-16 Hours	Strongly positive	Strongly positive		Weakly positive
24 Hours	Peaks	Peaks		Weakly positive
2 Days	Persists	Persists		Negative
3 Days	Negative	Persists	Peaks	
4-7 Days		Persists	Persists	

Rheumatic Fever

- Rheumatic fever is a multisystem inflammatory disorder with major cardiac manifestations and sequelae
- Which affects heart valves **in order of frequency**
    - *Mitral (fish mouth button hole deformity) > aortic > tricuspid (high-pressure valves affected most).*
    - *Early lesion is mitral valve regurgitation; late lesion is mitral stenosis*
- It usually occurs 1 to 4 weeks after an episode of pharyngitis caused by group-A β-hemolytic streptococci.
- Associated with *Carey coomb's murmur*
- Most often affecting children between 5 and 15 years of age.
- *It is type-2 hypersensitivity* reaction in which the antibodies develop against M-proteins of streptococci cross react with cardiac enzymes.
- **Aschoff bodies:**
    - *Pathognomonic and characteristic lesion of rheumatic fever*
    - Composed of multinucleated giant cells (Aschoff cells) surrounded by enlarged macrophages (Anitschkow cells) and T-lymphocytes.
- **Diagnostic criteria:**
    - *Jones criteria*
    - *It is positive if there is evidence of recent streptococcal infection (elevated ASO Titre) plus 2 major criteria OR 1 major + 2 minor criteria.*

Major criteria	Minor criteria
• Migratory polyarthritis (common initial)	• Fever
• Carditis (all 3 layers)	• Arthralgia
• Subcutaneous nodules (painless)	• Elevated ESR
• Skin rash (erythema marginatum	• First degree AV block
• Sydenham chorea (late manifestation)	• Leucocytosis

- Treatment/prophylaxis **Penicilin**

Rheumatic Fever: Criteria

Mnemonic: "JONES CAF PAL"

Major Criteria

J	Joint involvement
O	O looks like a g=heart = myocarditis
N	Nodules, subcutaneous
E	Erythema marginatum
S	Sydenham chorea

Minor Criteria

C	CRP Increased
A	Arthralgia
F	Fever
E	Elevated ESR
P	Prolonged PR Interval
A	Anamnesis of Rheumatism
L	Leukocytosis

Diagnosis

Throat cultures growing GABHS OR Elevated anti-streptolysin O titers + 2 Major criteria OR 1 Major criterion and 2 Minor criteria

Endocarditis

- Refers to microbial infection of endocardium of heart
- Marked by prominent involvement of the Valvular surfaces
- Valvular heart disease occurs often as a late result of rheumatic fever
- *Characteristics include large, soft, friable, easily detached vegetations.*
- **Classification:**

Acute Endocarditis	• *Staphylococcus aureus (50% of cases). Commonly involves tricuspid valve* Mnemonic: don't "tri" drugs • Tricuspid valve endocarditis is associated with IV drug abuse.
Sub-Acute (Bacterial) Endocarditis	• *Caused by Streptococcus viridans (**more than 50% of cases**). This type of endocarditis tends to occur in patients with congenital heart disease or preexisting valvular heart disease, often of rheumatic origin.*

Nonbacterial(Marantic/Thrombotic)	• *2° to malignancy, hypercoagulable state, or lupus*
Libman-Sacks Endocarditis	• *Occurs in systemic lupus erythematosus (SLE).* **(LSE in SLE)**
Other Forms	• *S. bovis (gallolyticus) is present in colon cancer* *S. epidermidis on prosthetic valves*

Valve involvement

- *Mitral valve > Aortic valve*
- *The tricuspid valve is involved in more than 50% of cases of endocarditis of intra- venous drug users, in whom endocarditis is most often caused by staphylococcal infection.*

Clinical features: (FROM JANE)

- **F**ever, **R**oth spots (retinal hemorrhages + pale center), **O**sler nodes (painful subcutaneous nodules in pulp of digits), **M**urmur
- **J**aneway lesions (small, painless, erythematous lesions on palm or sole), **A**nemia, **N**ail-bed haemorrhage, **E**mboli

Diagnosis

Modified Duke Criteria for the Diagnosis of Infective Endocarditis

Major criteria	Minor criteria	
3. *Positive blood cultures for IE* • Two separate blood cultures with viridans streptococci, Staphylococcus aureus, HACEK group . • Single positive blood culture for Coxiella burnetii 3. *Evidence of endocardial involvement/* Echocardiography (Echo):- * Change in valve mvm. * New regurg * Not as flexibly moving as prior healthy echo. heart. ⇒ if there's a prosthetic valve, IE would cause dehiscence of prosthetic valve (of v.)	1. Predisposing heart condition or intravenous drug use 2. Fever 38°C (100.4°F) 3. Vascular phenomena • Arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, **Janeway lesions** 4. Immunologic phenomena: • Arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, **Janeway lesions** 5. Microbiologic evidence • Positive blood culture but not meeting major criteria or serologic evidence of infection with an organism consistent with IE	**Definite diagnosis** • *2 major criteria **OR*** • *1 major and 3 minor criteria **OR*** • *5 minor criteria* **Possible diagnosis** • 1 major and 1 minor criteria **OR** 3 minor criteria

Treatment: Antibiotic (4 weeks) [Vancomycin / Gentamycin / Cipro / Rifampin]
↳ prosthetic valves.

Indications for surgery:

- Sever valvular incompetence, infections resistant to medical therapy, cardiac failure, recurrent emboli after antibiotic therapy
- Aortic abscess (often indicated by lengthening of PR interval)

Cardiac tamponade

- Compression of heart by fluid (e.g., blood, effusions) in pericardial space. ↓ CO.
- **Findings:**
  - ***Beck triad** (hypotension, distended neck veins, distant heart sounds)*
  - *↑HR.*
  - ***Pulsus paradoxus**—↓in amplitude of systolic BP by > 10 mmHg during inspiration. (Seen in cardiac tamponade, asthma, obstructive sleep apnea, pericarditis, croup)*
  - Lung fields are clear on exam.

- **Diagnosis:**
  - Echo is diagnostic and shows right atrial and right ventricular diastolic collapse
  - and echo-free zone around the heart.
  - CXR may show an enlarged, globular, water-bottle-shaped heart with a
  - large effusion
  - If present on ECG, electrical alternans is diagnostic of a large pericardial
  - effusion.
- **Treatment:**
  - Aggressive volume expansion with IV fluids.
  - Urgent pericardiocentesis (aspirate will be non-clotting blood). Send fluid to lab analysis to determine etiology.
  - Decompensation or recurrent cases may warrant pericardial window.

Pericarditis

- It refers to Inflammation of the pericardium

Clincial features:
  - *Sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward.*
  - *On examination:*
    - *Pericardial friction rub.*
    - Elevated JVP
    - Tachycardia,
    - *Muffled S1 and S2*, and
    - *Pulsus paradoxus (a ↓ in systolic BP >10 mm Hg on inspiration) can be present with pericardial tamponade.*
    - *Kussmaul sign can be present with constrictive pericarditis*
- **Causes**
  - *Idiopathic (most common), Viral (Coxsackievirus),* Autoimmune (eg, SLE, rheumatoid arthritis), acute STEMI or Dressler syndrome
- **ECG:**
  - *Widespred concave (saddle shaped) ST levation*
  - *PR depression= most specific ECG marker for pericarditis*
- **Echo:**
  - Pericardial thickening or effusion may be evident
- **Treatment:**
  - Treat the underlying cause (eg, corticosteroids/immunosuppressants for SLE, dialysis for uremia) or symptoms (eg, ASA for post-MI pericarditis, ASA/NSAIDs for viral pericarditis or Dressler syndrome).
  - Avoid corticosteroids within a few days after MI, as they can predispose to ventricular wall
  - rupture.
  - Treat idiopathic cases with NSAIDs such as ibuprofen, naproxen, or indomethacin.
  - Consider colchicine for relapse or persistent symptoms.
  - Pericardial effusions without symptoms can be monitored, but evidence of tamponade requires pericardiocentesis with continuous drainage as needed.

Valvular Heart Diseases

	Causes	Signs and symptoms	Murmur
Mitral Stenosis	• Rheumatic heart disease (most common cause), • Mitral annular calcification, • Malignant carcinoid	• Apex beat – localized, and tapping. • Heart sounds S1 is loud.	• *Opening snap* (presystolic accentuation) • Mid-diastolic murmur:
Mitral Regurgitation	• Rheumatic fever prevalent countries rheumatic heart disease (50%)	• Apex beat forceful, displaced with systolic thrill. Heart sounds soft S1; Split S2, Loud P2 (Pulmonary HTN)	• *High-pitched, blowing, pansystolic murmur at apex* Best heard at apex, radiates to axilla

	• Rheumatic fever prevalent countries rheumatic heart disease (50%)		
Mitral Valve Prolapse (also known as Myxomatous mitral valve disease, floppy valve syndrome)	• Idiopathic Familial (autosomal dominant) Marfans syndrome Ehler-Danlos syndrome	• ·Pain (atypical chest pain) — is the most common symptom. ·Palpitations Panic attacks	• High-Pitched. *mid-systolic click* — is the most common sign
Aortic Stenosis	• Calcific aortic valve stenosis (dystrophic calcification) — most common cause • Congenital abnormal unicuspid or bicuspid valve • Rheumatic heart disease	• **Angina (most common)** • Syncope • Apex beat —sustained • Heart sounds -----soft A2 • Pulse ----Slow-rising pulse with narrow pulse pressure	• Crescendo-decrescendo ejection systolic murmur • InaudibleA2 indicates severe AS • Radiates towards carotid
Aortic Regurgitation	• Acute: Infective endocarditis, Trauma, Aortic dissection • Chronic: Rheumatic fever, bicuspid aortic valve, Marfan syndrome, Ehlers-Danlos syndrome, ankylosing spondylitis, SLE	• Apex beat displaced, heaving. forceful • Pulse large volume, Collapsing (water-hammer) pulse—wide pulse pressure	• High-pitched early diastolic decrescendo murmur at left sternal border. • Austin-Flint murmur in severe AR

Ejection systolic:

Aortic stenosis, HOCM, pulmonary stenosis, ASD, Fallot's

Holosystolic (pansystolic)

Mitral/tricuspid regurgitation (high-pitched and 'blowing' in character)

VSD ('harsh' in character)

Late systolic:

Mitral valve prolapse (mid-systolic click — is the most common sign)

Coarctation of aorta

Early diastolic:

Aortic regurgitation (high-pitched and 'blowing' in character)

Graham-Steel murmur (pulmonary regurgitation, again high-pitched and 'blowing' in character)

Mid-late diastolic:

Mitral stenosis ('rumbling' in character)

Austin-Flint murmur (severe aortic regurgitation, again is 'rumbling' in character)

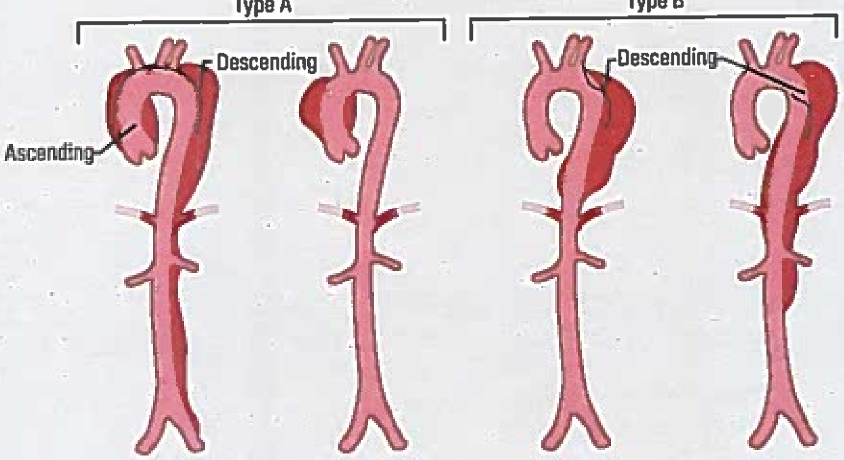
Continuous machine-like murmur: ----Patent ductus arteriosus (Murmur radiates to back)

Aortic Dissection

- A transverse tear in the intima of a vessel that results in blood entering the media, creating a false lumen and leading to a hematoma that propagates longitudinally.
- **Causes:**
  - *Secondary to HTN (Most Common)*
  - Blunt chest trauma.
- **Site of Origin**
  - *The most common sites of origin are above the aortic valve and distal to the left subclavian artery.*
- **Gender/ Age**
  - Most often occurs at 40-60 years of age, with a greater frequency in males than in females.
- **Presentation:**

- *Sudden tearing/ripping pain in the anterior chest (ascending) with or without radiation to the back (descending), typically between the scapulae.*
- Asymmetric pulses and BP measurements or acute limb ischemia

- **Diagnosis:**
    - Best initial test for hemodynamically stable patients
        - *CT angiography.*
        - MRA can be used if contrast CT is contraindicated
    - Best initial test for hemodynamically unstable patients:
        - TEE. It may also be used to visualize details of the proximal aorta and coronary vessels and can also evaluate for pericardial effusion
- **Classification:**
    - The Stanford system classifies any dissection proximal to the left subclavian artery as type A and all others as type B
    - Type A (70%) is the most common and involves the ascending aorta, irrespective of the site of the tear.
    - Type B does not involve the ascending aorta.



Standford classification of aortic dissection. Type A involves the ascending aorta and may progress to involve the arch and thoracoabdominal aorta. Type B involves the descending thoracic or thoracoabdominal aorta distal to the left subclavian artery without involvement of the ascending aorta.

- **Treatment:**
    - BP control:
    - *Begin intravenous β-blockers (eg. IV labetalol) before starting vasodilators (nitroprusside) to prevent reflex tachycardia.*
    - Avoid thrombolytics.
    - All patients with type A thoracic dissection (ascending dissections) should have surgery.
    - Patients with type B thoracic dissection (descending dissections) may be managed medically with BP and heart rate control; surgery is reserved if there is a leakage, rupture, or compromised organs.

Cyanotic Heart Diseases: (4 T's)

❖ Right- to-Left shunts- eaRLy cyanosis, blue babies

Truncus arteriosus	• Truncus arteriosus fails to divide into pulmonary trunk and aorta due to lack of Aorticopulmonary septum formation Most patients have accompanying VSD.
Transposition of great vessels	• Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) Not compatible with life unless a shunt is present to allow mixing of blood (e.g., VSD, PDA, or patent foramen ovale) *Most common cause of cyanosis overall at birth*

Tricuspid atresia	• Absence of tricuspid valve and hypoplastic RV; requires both ASD and VSD for viability.

Tetralogy of Fallot (mnemonic-PROVe)	• *Most common cause of early childhood cyanosis* **(does not usually present until 1-2 months therefore TGA is most common at birth)**
	• Features include
	  ▪ **P**ulmonary infundibular stenosis (most important determinant for prognosis)
	  ▪ **R**ight ventricular hypertrophy (RVH)— *boot-shaped heart on CXR*
	  ▪ **O**verriding aorta
	  ▪ **V**SD
	• Tendency of patients to assume a squatting position, presumably because of lessening of right-to-left shunting

Ebstein's anomaly	• A congenital heart defect characterised by low insertion of the tricuspid valve resulting in a large atrium and small ventricle. • It is sometimes referred to as 'atrialisation' of the right ventricle. • Ebstein's anomaly may be caused by exposure to lithium in-utero

Non-Cyanotic Heart Disease

- Late cyanosis
- VSD > ASD > PDA
- No shunts: Coarctation of aorta, aortic stenosis,
- Left-to-Right shunts: "LateR" cyanosis.
  - Patent ductus arteriosus,
  - Atrial septal defect
  - *Ventricular septal defect (most common)*

Ventricular septal defect	• Small defects may close spontaneously • Larger defects may lead to pulmonary hypertension and eventual right-sided heart failure
Atrial septal defect	• Defect in interatrial septum Loud S1; wide, fixed split S2.
Patent ductus arteriosus	• *Failure of closure of the fetal ductus arteriosus* • *Associated with a continuous, "machine-like" murmur.* • *Patency is maintained during fetal life by PG-E synthesis and low O_2 tension.* • Can be closed surgically or pharmacologically treated with indomethacin • PDA is normal in utero and normally closes only after birth
Coarctation of aorta	• Narrowing of the aorta, usually distal to the origin of the subclavian arteries • ***Hypertension in upper extremities and weak delayed pulse in lower extremities (brachial-femoral delay).*** • *With age, collateral arteries erode ribs (notched appearance on CXR).*
Eisenmenger's syndrome	• The reversal of a left-to-right shunt in a congenital heart defect due to pulmonary HTN. This occurs when an uncorrected left-to-right leads to remodeling of the pulmonary microvasculature, eventually causing obstruction to pulmonary blood and pulmonary hypertension.

Congenital Cardiac Defect Associations

Alcohol Exposure In Utero (Fetal Alcohol Syndrome)	• VSD, PDA, ASD, tetralogy of Fallot
Congenital Rubella	• Septal defects, *PDA*, pulmonary artery stenosis
Down Syndrome Trisomy 21	• *AV septal defect* (endocardial cushion defect), VSD, ASD

Infant Of Diabetic Mother	• *Transposition of great vessels*
Marfan Syndrome	• *Thoracic aortic aneurysm and dissection, aortic regurgitation, MVP*
Turner Syndrome -XO	• Bicuspid aortic valve, Coarctation of aorta
Fragile X	• Mitral valve prolapse, aortic root dilatation
Noonan Syndrome	• Pulmonary stenosis with dysplastic pulmonary valve

Cardiomyopathy

- This term refers to diseases of the heart muscle that are *noninflammatory and are not associated with hypertension, congenital heart disease, valvular disease, or coronary artery disease.*
- Usually, these diseases are characterized by otherwise unexplained ventricular dysfunction (heart failure unresponsive to digitalis, ventricular enlargement, ventricular arrhythmias).
- It occurs in several forms

Congestive Or Dilated Cardiomyopathy	• *Most common cardiomyopathy* (90% of cases). Often idiopathic or familial. Other etiologies include: (**ABCD-P**) ◦ **A**lcohol abuse (chronic) ◦ ***B₁-Thiamine deficiency (beriberi heart-wet Beriberi)*** ◦ **C**oxsackie B virus myocarditis. ◦ **D**oxorubicin toxicity ◦ **P**eripartum cardiomyopathy (associated with the latter stages of **p**regnancy) • Findings: HF, S3 heart sound, mitral regurgitation, *balloon appearance of heart on CXR.* Treatment: Na+ restriction, ACE inhibitors, β-blockers, diuretics, digoxin, ICD, heart transplant
Restrictive Cardiomyopathy	• The cause is infiltrative processes within the myocardium that result in stiffening of the heart muscle, which interferes with pumping action. • This cardiomyopathy is exemplified by *cardiac amyloidosis*, which may result in both right- and left-sided heart failure
Hypertrophic Cardiomyopathy	• *Autosomal dominant characteristic (commonly a β-myosin heavy-chain mutation).* • Gross characteristics include hypertrophy of all chamber walls, especially the ventricular septum (asymmetric septal hypertrophy). • *Cardiomyopathy may result in left ventricular outflow obstruction, placing the patient in danger of syncope and even **sudden death**, which often occurs unexpectedly in **young athletes*** • Echo: (mnemonic: **MR SAM ASH**) ◦ **M**itral **R**egurgitation (**MR**) ◦ **S**ystolic **A**nterior **M**otion (**SAM**) of mitral valve ◦ **AS**ymmetric **H**ypertrophy (**ASH**) • ECG: ◦ LVH + T Wave Inversion • Treatment: ◦ *β-blockers (1st line)* ◦ Non-dihydropyridine CCBs (2nd Line) ◦ *Digoxin and spironolactone are contraindicated.* ◦ Implantable defibrillators should be used in symptomatic ◦ Surgical excision or alcohol ablation

Heart Failure

- Congestive heart failure may be failure of the left ventricle, right ventricle, or both.
- This condition often presents with dyspnea and/or edema.

  Assay of B-type natriuretic peptide (BNP), which is elevated in heart failure, can aid in the distinction of heart failure from a number of other conditions such as asthma, acute coronary syndrome, chronic obstructive pulmonary disease, or pulmonary embolism, which can also present with dyspnea or edema

Left heart failure	Right heart failure
Causes: • **Ischemic heart disease (especially myocardial infarction)** • Hypertension • Aortic and mitral valvular disease • Myocardial diseases, such as cardiomyopathies and myocarditis	Causes: • *Left-sided heart failure is the most common cause of right-sided heart failure.* *Cor-pulmonale: (dilation secondary to lung disease or primary disease of the pulmonary vasculature, such as primary pulmonary hypertension. Emphysema is a frequent cause)*
Clinical manifestations: • Dyspnea and orthopnoea caused by pulmonary congestion and edema regularly occurs • *Pulmonary edema: Presence of hemosiderin-laden macrophages (HF-cells) in lungs* • *Reduction in renal perfusion, causing activation of the renin-angiotensin-aldosterone system and leading to retention of salt and water, but is less frequent* • Cerebral anoxia is less frequent • Distention of neck veins	Clinical manifestations: • *Renal hypoxia, leading to greater fluid retention and peripheral edema than seen in left-sided failure.* • Enlarged and congested liver and spleen. • *Chronic passive congestion of the centrilobular veins of the liver surrounded by relatively pale, sometimes fatty, peripheral regions leads to a **"nutmeg"** pattern.* • Distention of the neck veins

Management:

- Drugs known to improve mortality
  - ACE inhibitors
  - Spironolactone
  - Beta blockers—such as carvedilol and bisoprolol
  - Hydralazine with nitrates
- No long-term reduction in mortality with loop diuretics such as furosemide

Cardiac tumors

- **Primary tumors**
  - Myxoma of the left atrium is the most frequently occurring cardiac tumor and is found most often in adults; it is benign.
  - *Rhabdomyoma is most common in infants and young children and is notable for its association with tuberous sclerosis*; it is benign.
  - Angiosarcoma is the most common primary malignancy of the heart.
- **Metastatic tumors**
  - Are more frequent than primary tumors

Note: Most common heart tumor is a metastasis (e.g., melanoma).

Lipoprotein functions

- Lipoproteins are composed of varying proportions of cholesterol, TGs, and phospholipids. LDL and HDL carry the most cholesterol.

Chylomicron	• Delivers dietary TGs to peripheral tissues. • Delivers cholesterol to liver in the form of chylomicron remnants, which are mostly depleted of their TGs. • Secreted by intestinal epithelial cells
Cholesterol	• Needed to maintain cell membrane integrity and synthesize bile acid, steroids, and vitamin D.
HDL	• HDL is good because it carries extra cholesterol back to the liver where it can be eliminated. • **Mnemonic: H**DL is **H**ealthy
LDL	HDL is good because it carries extra cholesterol back to the liver where it can be eliminated. **Mnemonic: H**DL is **H**ealthy
VLDL	• Delivers hepatic TGs to peripheral tissue. Secreted by liver.

Hyperlipidemia

- Hyperlipidemia is abnormally elevated levels of any or all lipids or lipoproteins in the blood
- Classification
  - Primary (aka familial)---- caused by specific genetic abnormalities
  - Secondary or Acquired--- when resulting from another underlying disorder e.g DM, hypothyroidism, obesity, Alcohol, Drugs (thiazide diuretics, Beta blockers, Estrogen)

Familial (primary)

- Familial hyperlipidemias are classified according to the Fredrickson classification

Type	Inheritence	Sub type	Synonyms	Defect	↑Blood Level	Main symptoms
TYPE I	AR	a	Familial hyperchylomicronemia	Decreased lipoprotein lipase (LPL)	• Chylomicrons • TG • cholesterol	• *Acute pancreatitis* • *Eruptive skin xanthomas* • Hepatosplenomegaly • No↑risk for atherosclerosis.
		b	Familial apoprotein CII deficiency	Apolipoprotein C-II deficiency		
Type II	AD	a	Familial hypercholesterolemia	LDL receptor deficiency	• Cholesterol LDL	• *Accelerated atherosclerosis (may have MI before age 20), Tendon (Achilles) xanthomas* Corneal arcus.
		b	Familial combined hyperlipidemia	Decreased LDL receptor and increased ApoB	• Cholesterol • LDL • VLDL	
Type III	AR		Familial dysbetalipoproteinemia	Defect in Apo E2 synthesis	• Chylomicrons • VLDL	• Premature atherosclerosis, • tuberoeruptive xanthomas, • Xanthoma striatum palmare.
Type IV	AD		Familial hypertriglyceridemia	Increased VLDL production and decreased elimination	• VLDL • TG	• Hypertriglyceridemia (> 1000 mg/dL) can cause acute pancreatitis.

Hyperlipidemia signs/xanthomas associated with hyperlipidemias

Xanthomas variant	Description	Examples/Association
Xanthomas/ xanthelasma 	• Yellowish collection of cholesterol underneath the skin, usually on or around the eyelids	• Type II Type III
Eruptive Xanthoma 	• Are due to high TG levels and • Present as multiple red/yellow vesicles on the extensor surfaces (e.g. Elbows, knees)	• Type I hyperlipidaemia
Palmar Xanthoma 	• Yellowish plaques that involve the palms and flexural surfaces of the fingers	• Type III • Less commonly in (type IIa)
Tuberous Xanthoma 	• *Characterized by xanthomas located over the joints*	• *Type III*
Tendon Xanthoma 	• *Commonly affect the Achilles tendons & Tendons overlying the metacarpophalangeal joints In the hands.*	• *Familial hypercholes terolaemia (Type iia*

Different Type of Pulses

Pulse Type	Definition	Examples
Pulsus paradoxus	• *>10mmHg fall in systolic blood pressure during inspiration---faint or absent pulse on inspiration*	• *Cardiac tamponade* *Severe asthma*
Slow rising pulses (Pulsus parvus et tardus)	• *This wave form is characterised by a slow upstroke.*	• *Aortic stenosis*
Collapsing pulse (Water-hammer pulse)	• Is a large bounding pulse associated with increased stroke volume of the left ventricle and decrease in the peripheral resistance, leading to a wide pulse pressure The pulse strikes the palpating finger with a rapid, forceful jerk and quickly disappears	• *Aortic regurgitation* *Patent ductus arteriosus* Hyperkinetic (anemia, thyrotoxic, fever, exercise/ pregnancy)

Pulsus alternans	• Pulsus alternans is characterized by a strong and weak beat occurring alternately, probably due to alternate rather than regular contraction of the muscle fibres of the left ventricle.	• *Severe LVF*
Pulsus bisferiens	• Pulsus bisferiens is a rapid rising, twice beating pulse	• Aortic valve disease
Jerky pulse	• Rapid upstroke due to the vigorous contraction of the hypertrophic left ventricle	• *HOCM*
Radio-Femoral Delay	• Delay of the femoral pulse as compared with the radial pulse	• *Coarctation of aorta*
Radio-Radial delay	• Delay of the radial pulse on one side as compared with the radial pulse of the other side	• Thoracic inlet syndrome e.g cervical rib pressing on the subclavian artery of one arm, delaying the radial pulse on that side. • Dissecting thoracic aorta • Aortic aneurysm

Quick points

Holiday heart syndrome	• SVT due to alcohol intake in persons who are otherwise healthy
O_2 saturation	• 70% in RA, RV, Pulmonary artery • 98-100% in LA, LV, & Aorta
MUGA scan	• **Multi Gated Acquisition Scan**, also known as radionuclide angiography • Radionuclide (technetium 99m) is injected intravenously and then **measure left ventricular ejection fraction at rest and stress** • **Typically used before and after cardiotoxic drugs**
Cardiac CT	• For assessing ischemic heart disease • CT There is known to be a correlation between the amount of atherosclerotic plaque calcium and the risk of future **ischaemic events**

Cardiac MRI (aka CMR)	• Cardiac MRI has become the gold standard for providing structural images of the heart.
	• It is particularly useful when:
	  ◦ Assessing congenital heart disease,
	  ◦ Determining right and left ventricular mass and
	  ◦ Differentiating forms of cardiomyopathy.

Chapter 4: Respiratory System

UPPER RESPIRATORY TRACT

Disorders of Upper Respiratory System

Acute Rhinitis	• Common cold
	  ◦ Most common (most commonly by viruses, especially the adenoviruses). It is manifest by coryza ("runny nose"), sneezing, nasal congestion, and mild sore throat.
	• Allergic rhinitis
	  ◦ IgE type I immune reaction and Increased eosinophil's

Sinusitis	• Inflammation of the paranasal sinuses. Obstructed drainage outlets from the sinuses Leading to an accumulation of mucoid secretions or exudate
Laryngitis	• Acute inflammation of the larynx (viruses, bacteria, overuse of the voice) Inflammation, edema of the vocal cords, *Hoarseness.*

Acute Epiglottitis	• Inflammation of the epiglottis (life-threatening)
	It is usually caused by H. Influenza.
	Diagnosis:
	  ◦ Laryngoscopy--- **direct visualization of cherry red swollen epiglottis**
	  *X- ray neck (lateral view) ---**Thumb sign***
	• Treatment:
	  ◦ Epiglottitis is a medical emergency.
	  ◦ Nasotracheal intubation
	  ◦ Third-generation cephalosporin (ceftriaxone).
	  ◦ If epiglottitis is secondary to HIB, Rifampin prophylaxis is indicated for unimmunized household contacts Younger than 4 years of age.

Acute Laryngotracheobronchitis (Croup)	• Acute inflammation of the larynx, trachea, and epiglottis **Barking cough and inspiratory stridor.** ***Steeple sign** on x-ray* *Pulsus paradoxus 2° to upper airway obstruction* Treatment: None or nebulized epinephrine if severe Parenteral steroid

Thumb sign (Epiglottitis)

Steeple sign (Croup)

Obstructive Lung Disease

- Group of disorders characterized by airflow obstruction
- *Characteristics include a marked decrease in the 1-second forced expiratory volume (FEV_1) and an increased or normal forced vital capacity (FVC), resulting in a decreased FEV_1:FVC ratio. (FEV_1: FVC <70%)*
- **COPD**
- *In restrictive lung disease, the FEV_1 and FVC are both decreased proportionately, resulting in a normal FEV_1: FVC ratio.*

Disease	Types /definition	Pathology	Characteristics
Bronchial asthma	**Extrinsic (immune) asthma**	• Type-1 hypersensitivity response (IgE) • Disease begins in childhood • Family history of allergy. • Bronchial Smooth muscle hypertrophy and Hyperplasia of submucosal glands	• Cough, dyspnea • *Wheezing* • Tachypnea • Hypoxemia. • *Pulsus paradoxus*
	Intrinsic asthma	• Asthma associated with chronic bronchitis, as well as other asthma variants such as exercise- or cold induced asthma. • It usually begins in adult life • No family history of allergy • Hyperplasia of submucosal glands, ↑REID index	• Status asthmaticus, a prolonged bout of bronchial asthma that can last for days and that responds poorly to therapy
Chronic Bronchitis ("Blue Bloater")	Productive cough for > 3 months per year (not necessarily consecutive) for >2 years.	• Hypersecretion of mucus due to marked hyperplasia of mucus-secreting Submucosal glands • Linked to cigarette smoking	• Crackles Cyanosis CO_2 retention (hypercapnia) *2° polycythemia.*
C O P **EmPhysema ("Pink Puffer")** Dilation of air spaces with destruction of alveolar walls and lack of elastic recoil	**Centriacinar** (*Associated strongly with **SMOK**ing*, affects <u>**UP**</u>per lobes) (sm<u>**OK**</u>e rises <u>**UP**</u>) **Panacinar** (*Associated with α-1 antitrypsin deficiency.* affects entire acinus upto terminal bronchioles)	• ↑Elastase activity loss of elastic fibers ↑lung compliance • Cigarette smoking attracts neutrophils and macrophages, which are sources of elastase. • *It is strongly associated with smoking*	• Exhalation through pursed lips to ↑airway pressure and prevent airway collapse during respiration. • Barrel-shaped chest

Bronchiectasis		• *Chronic necrotizing infection of bronchi permanently dilated airways,* purulent sputum, recurrent infections, *hemoptysis* *Lower lobes mostly affected* *Diagnosis:* ***HRCT***	• Associated with bronchial obstruction • *Poor ciliary motility (e.g., smoking, Kartagener syndrome)* • **Cystic fibrosis** • Bronchopulmonary aspergillosis • Panhypogammaglobulienemia

Management of Asthma

Step 1:	Inhaled short-acting B2 agonist as required
Step 2	Add inhaled steroid at 200-800 mcg/day (400 mcg is an appropriate starting dose)
Step 3	Add inhaled long-acting B2 agonist (LABA) Assess control of asthma • Good response to LABA continue LABA • **Benefit** from LABA but **control still inadequate** continue LABA and increase inhaled • steroid dose to 800 mcg/day No response to LABA • Stop LABA and Increase inhaled steroid to 800 mcg/ day If control still inadequate, institute trial of other therapies leukotriene receptor antagonist or SR theophylline
Step 4	Consider trials of: • Stop LABA and Increase inhaled steroid to 800 mcg/ day If control still inadequate, institute trial of other therapies leukotriene receptor antagonist or SR theophylline Leukotriene receptor antagonist, SR theophylline,
Step 5	Use daily steroid tablet in lowest dose providing adequate control. Consider other treatments to minimize the use of steroid tablets • Maintain high dose inhaled steroid at 2000 mcg/day*

Cystic Fibrosis

- ***Autosomal recessive***
- CF is a multisystem disorder that results in altered content of exocrine gland secretions.
- *It is caused by* ***mutation of CFTR (Cystic Fibrosis Transmembrane conductance Regulator)*** *located on long arm of chromosome 7* (CFTR normally maintains hydration of exocrine organ secretions & regulates transport of electrolytes across the epithelium)

Clinical features:

Respiratory Symptoms:	Gastrointestinal Symptoms
• Chronic cough • ***Recurrent pneumonia*** *(first with Staphylococcus aureus, and later with Pseudomonas aeruginosa)* • ***Nasal polyps*** • Chronic pan sinusitis	• ***Pancreatic insufficiency*** *occurs in 85% of patients.* • Meconium ileus (15% to 20% of patients present with this symptoms). • Pancreatitis • Rectal Prolapse

Diagnosis requires:

Any of the Following	Plus Any of the Following
• Typical clinical features • History of a sibling with CF • Positive new-born screen	• Sweat chloride test: *Two increased sweat chlorides on 2 separate days* ***(>60 mmol/L is positive for CF)*** • CFTR gene mutation Identification of 2 CF mutations (homozygous) • Increased nasal potential difference

Treatment:

- Vaccination--- Against pneumococcal infection and annual influenza vaccination
- High calorie and high fat diet, Pancreatic enzyme replacement FOR EVERY MEAL
- Antibiotics: *most common organisms are S. aureus and Pseudomonas aeruginosa*
- Definitive treatment: **Lung transplantation**

Quick review mnemonic: CF PANCREAS

- **C**hronic respiratory diseases occur, **F**ailure to thrive, **P**ancreatic exocrine and endocrine insufficiency, **A**utosomal recessive inheritance, **N**eonatal intestinal obstruction
- **C**lubbing of fingers, **C**holestasis, biliary **C**irrhosis
- **R**ectal prolapse, **E**lectrolyte excess in sweat like sweat Na+ and C, **A**zoospermia and infertility
- **S**taph aureus and p**S**eudomonas in sputum, **S**alty sweat

Restrictive Pulmonary Diseases

- Restricted lung expansion causes ↓ lung volumes (↓FVC and TLC). *FEV_1/FVC ratio ≥ 80%.*
- Types:
  - **Poor breathing mechanics** (bony abnormalities, neuromuscular disease normal A-a gradient):
    - Poor muscular effort—polio, myasthenia gravis
    - Poor structural apparatus—scoliosis, morbid obesity
  - **Interstitial lung diseases** (pulmonary↓diffusing capacity,↑A-a gradient):
    - In ILD think **FASSTEN** and **BAD RASH**
    - Upper Lung Disease (**FASSTEN**)
      - **F**armer's lung (hypersensitivity pneumonitis/Extrinsic allergic alveolitis)
      - **A**nkylosing spondylitis
      - **S**arcoidosis
      - **S**ilicosis
      - **T**B
      - **E**osinophilic granuloma (Langerhans-cell histiocytosis),
      - **N**eurofibromatosis
  - Lower Lung Disease (**BADRASH**)
      - **B**ronchiolitis obliterans with organizing pneumonia (BOOP)
      - **A**sbestosis
      - **D**rugs (nitrofurantoin, hydralazine, INH, amiodarone, methotrexate,many chemo drugs)
      - **R**heumatologic disease (SLE, RA, Scleroderma)
      - **A**spiration
      - **S**cleroderma
      - **H**amman Rich (acute interstitial pneumonia) and IPF

Respiratory Distress Syndrome:

	Adult Respiratory Distress Syndrome	Neonatal Respiratory Distress Syndrome
Definition	*Diffuse alveolar damage→↑alveolar capillary permeability protein-rich fluid leakage into alveoli and non-cardiogenic pulmonary edema (normal PCWP)*	*Also known as Hyaline Membrane Disease. Most common cause of respiratory failure in the newborn and is the most common cause of death in premature infants due to surfactant deficiency.*
Causes	Shock, sepsis, trauma, uremia, aspiration of gastric contents, oxygen toxicity, near drowning, or overdose with street drugs such as heroin	*Surfactant deficiency→↑surface tension→ alveolar collapse ("ground-glass" appearance of lung fields)*
Explanation	ARDS can be a manifestation of the severe acute respiratory syndrome (SARS). The SARS virus is a coronavirus that destroys type II pneumocytes and causes diffuse alveolar damage. ***↓PaO2/FiO2 < 300*** *(hypoxemia due to↑ intrapulmonary shunting and diffusion abnormalities).*	***Lecithin: sphingomyelin ratio < 1.5 in amniotic fluid is predictive of NRDS.*** Complications: • *Metabolic acidosis* • *PDA→due to Persistently low O_2 tension* • *Necrotizing enterocolitis.* Risk factors: • *Prematurity* • *Maternal diabetes (due↑tofetal insulin)* • *C-section delivery (↓release of fetal* • *glucocorticoids).*
Management	Mechanical Ventilation With Low Tidal Volumes, Address Underlying Cause	• Maternal Steroids Before Birth • Artificial Surfactant For Infant

Restrictive Pulmonary Diseases (Continued)

Diseases Associated with Inorganic Dusts

Pneumoconioses

- Environmental diseases are caused by inhalation of inorganic dust particles.
- *Increase risk of Cor-pulmonale and Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules)*
- ***Asbestos*** *is from the* ***roof*** *(was common in insulation), but affects the* ***base*** *(lower lobes).*
- ***Silica*** *and* ***coal*** *are from the* ***base*** *(earth), but affect the* ***roof*** *(upper lobes).*

Asbestosis	• *Associated with shipbuilding, roofing, plumbing* • ***Affects lower lobes*** • Characterized by ferruginous bodies (yellow-brown, rod-shaped bodies with clubbed ends resembling dumbbells that stain positively with Prussian blue; found in alveolar septum.) • "Ivory white," calcified, supradiaphragmatic and pleural plaques are pathognomonic of asbestosis • *Associated with ↑incidence of lung cancer (bronchogenic carcinoma > mesothelioma).* Smoking (10% risk) and asbestos (5%) are synergistic, i.e. a smoker with asbestos exposure has a 10 * 5 = **50 times** increased risk
Berylliosis	• Affects upper lobes Associated with exposure to **beryllium in aerospace and manufacturing industries.** Granulomatous on histology and therefore occasionally responsive to steroids.
Anthracosis	• Inhalation of carbon dust, Endemic in urban areas and causes no harm

Coal workers' pneumoconiosis	• Affects upper lobes • Inhalation of coal dust, which contains both carbon and silica, Also known as black lung disease.
Silicosis	• *Affects upper lobes* • *Associated with glass manufacturers, and stone cutters. Sandblasting, mines.* • Macrophages respond to silica and release fibrogenic factors, leading to fibrosis. • *It is thought that silica may disrupt phagolysosomes and impair macrophages,* ***increasing susceptibility to TB.*** • "Eggshell" calcification of hilar lymph nodes

Restrictive Pulmonary Diseases (Continued)

Diseases Associated with Organic Dusts

1. Sarcoidosis

- *Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology that is characterised by the presence of* ***non-caseating granulomas***
- **Epidemiology:**
  - Presentation age: 20-40 years
  - Female > male
  - More common in African, black Americans and northern Europe
- **Clinical findings:**
  - **Multisystem disorder** but most commonly affects lung

Lungs	• Most common (90%) • Often asymptomatic, chest examination often normal • Cough, Dyspnea, chest pain, • *Bilateral hilar lymphadenopathy*

Common Extra Pulmonary Manifestations	• Skin:
	  · ***Erythema nodosum**---painful purplish nodules usually occurring on shins*
	  · **Lupus pernio** ---erythematous & plaques located symmetrically over nose, cheeks and ears
	• CVS: cardiac arrhythmias, heart block, sudden death
	Eye:
	  · Anterior or posterior uveitis (dark spots that float in the visual field, blurred vision, red eyes may be)
	  · Sicca syndrome
	• Peripheral lymphadenopathy
	Hepatomegaly ± splenomegaly

Less common extra-pulmonary manifestations	• Kidneys: Nephrocalicinosis, Renal stones CNS: space occupying lesion, cranial nerve palsies, diabetes insipidus Bone: arthralgia and joint involvement

Two acute sarcoid syndromes	• **Lofgren's syndrome:**
	  · *Fever, erythema nodosum, bilateral hilar lymphadenopathy, arthralgias*
	• **Heerfordt-Waldenstrom syndrome:**
	  · Fever, parotid enlargement, anterior uveitis, facial nerve palsy

Investigations:

- *Definitive Diagnosis: Tissue biopsy/ Transbronchial lung biopsy, (lung, liver, lymph nodes, skin nodules, or lacrimal glands) is diagnostic and shows non-caseating granulomata*
- *Serum Ca2+, 24 hr. urinary Ca2+ ---Increased,---due to increased formation of calcitriol*
- *Elevated serum ACE in about~60%* **(non-specific, non-sensitive)**
- CXR is abnormal in 90%: (CXR changes in Sarcoidosis can be staged)

Stage I	Bilateral Hilar Lymphadenopathy (BHL)
Stage II	BHL + Peripheral Pulmonary Infiltrates.
Stage III	Peripheral Pulmonary Infiltrates Alone
Stage III	Peripheral Pulmonary Infiltrates Alone

Clinical Pearls

Hypercalcemia might suggest lung cancer as well as Sarcoidosis

2. Hypersensitivity Pneumonitis (aka Extrinsic allergic alveolitis)

- Due to inhalation of organic dust particles
  It is thought to be largely caused by immune-complex mediated tissue damage (type III hypersensitivity) although delayed hypersensitivity (type IV) is also thought to play a role in EAA, especially in the chronic phase
- **Types**

Disorder	Source	Antigen/Agent
Farmers lung	• Mouldy hay	• Micropolyspora faeni Aspergillus fumigatus Saccharopolyspora rectivirgula
Bird fancier's lung	• Avian excreta, proteins and feathers	• Avian serum proteins
Byssinosis	• Textile industries	• Cotton, flax, hemp dust
Inhalation ('humidifier') fever	• Contamination of air conditioning	• Thermophilic actinomycetes
Malt workers		• Aspergillus clavatus

- **Clinical features:**
  - Recurrent episodes of fever, malaise, headache, cough, dyspnea, Leucocytosis
- **Investigation:**
  - Chest x-ray: upper/mid-zone fibrosis
  - Broncho alveolar lavage (BAL): lymphocytosis
  - Blood: ***NO eosinophilia***
    - (exception Allergic bronchopulmonary aspergillosis (ABPA)—hypersensitivity response to Aspergillus growing in lung mucus. Associated with asthma and cystic fibrosis; may cause bronchiectasis and eosinophilia)
- **Treatment:**
  - Remove exposure to causative agent, Give oxygen if needed
  - In severe acute or protracted cases, oral corticosteroids (prednisone, 0.5 mg/kg daily as a single morning dose for 2 weeks, tapered to nil over 4-6 weeks

3. Eosinophilic granuloma

- *Characteristic cytoplasmic inclusions (birbeck granules) resembling tennis rackets*

4. Goodpasture syndrome

- Hemorrhagic pneumonitis and glomerulonephritis caused by antibodies directed against glomerular basement membranes

Pneumonia

- Inflammation of pulmonary parenchyma.
- Characterized by chills and fever, productive cough, blood-tinged or rusty sputum, pleuritic pain, hypoxia with shortness of breath, and sometimes cyanosis.
- If bacterial, it is most characteristically associated with neutrophilic leucocytosis with an increase in band neutrophils ("shift-to-the-left").

Morphologic Types of Pneumonia.

Lobar	• S. pneumoniae (most frequently) • Legionella • Klebsiella	• Involve entire lobe or lung • Intra-alveolar exudate→consolidation
Bronchopneumonia	• S. pneumoniae • S. aureus • H. influenzae • Klebsiella	• Patchy distribution involving ≥ 1 lobe Acute inflammatory infiltrates from bronchioles into adjacent alveoli
Interstitial (atypical) pneumonia	• Viruses (influenza, CMV, RSV, adenoviruses) (most common pneumonia in children—measles virus produce giant cell pneumonia) • Mycoplasma (most common interstitial overall) • Legionella • Chlamydia	• Diffuse distribution involving ≥ 1 lobe • Diffuse patchy inflammation localized to interstitial areas at alveolar walls • Generally follows a more indolent course ("walking" pneumonia).

Community Acquired Pneumonia	Hospital Acquired Pneumonia (Nosocomial Pneumonia)
Pneumonia occurring before or within 48 hours of hospital admission Agents: • *Streptococcus pneumonia (most common)* • H. Influenza • Staphylococcus aureus	Pneumonia occurring after 48 hours of hospital admission Agents: • *S aureus (both MSSA & MRSA)—most common* • *P aeruginosa (most common)* • E. coli • Ventilator Associated Pneumonia patients (Acinetobacter species and Stenotrophomonas maltophilia)

Severity of Pneumonia and Admission Criteria for Pneumonia

CURB-65 score		
C	Confusion present (abbreviated mental test score <8/10)	
U	(Plasma) urea level >7 mmol/L (126 mg/dl)	
R	Respiratory rate >30/min	
B	Systolic BP <90 mmHg; diastolic BP <60 mmHg Mortality rates increase with increasing score	
65	Age >65	
Calculation	1. point for each of the above; • Score 0-1: Treat as outpatient	• **Oral amoxicillin alone**
	• Score 2: Admit to hospital	• **Amoxicillin + clarithromycin (doxycycline if penicillin allergic)**
	• Score 3+: Often require ICU care	• **IV co-amoxiclav + clarithromycin OR** • **cefuroxime (Zinacef) + clarithromycin OR** • **cefotaxime (claforan) + clarithromycin**

Organism Specific Pneumonia Characteristics

Streptococcus pneumonia	• Gram positive, lancet shaped diplococcus, **Rust colour sputum** • **Most common cause of CAP** • *More common in elderly, alcoholics, post-splenectomy, immunosuppressed,* • *and patients with chronic heart failure or pre-existing lung disease* • Treatment -- amoxicillin, benzylpenicillin, or cephalosporin
Staphylococcal aureus	• *Most common cause of pneumonia post influenza* • *Association - intravenous drug users, or patients with underlying disease, e.g. leukaemia, lymphoma, cystic fibrosis (CF)*

Klebsiella pneumonia	• Is rare.
	• 5 A's of KlebsiellA:
	  ◦ *Aspiration pneumonia (in Alcoholics and DiAbetics)*
	  ◦ Abscess in lungs and liver
	  ◦ "Curr-A-nt jelly" sputum (blood/mucus)
	• Treatment: cefotaxime or imipenem.

Pseudomonas aeruginosa	• Green sputum **Most common cause of nosocomial pneumonia** ***Most common pathogen in bronchiectasis and CF*** *Most common cause of death due to pneumonia in patients with cystic fibrosis*
Mycoplasma pneumonia	• Bacteria with no cell wall, (therefore penicillin not useful against it) • Occurs in epidemics about every 4yrs. • It presents insidiously with flu-like symptoms (headache, myalgia, arthralgia) followed by a dry cough. • Diagnosis: PCR sputum or Mycoplasma serology. • **Cold agglutinins may cause an autoimmune haemolytic anaemia.** • Complications: skin rash (erythema multiforme, Stevens-Johnson syndrome, meningoencephalitis or myelitis), **Guillain-Barré syndrome.** • Treatment: Clarithromycin (500mg/12h) or doxycycline (200mg loading then 100mg OD) or a fluroquinolone (e.g. ciprofloxacin).

Legionella pneumophilia	• **Colonizes water tanks kept at <60°C (e.g. hotel air-conditioning and hot water systems) causing outbreaks of Legionnaire's disease.**
	• Flu-like symptoms (fever, malaise, and myalgia) precede a dry cough and dyspnoea.
	• Extra-pulmonary features include
	  ◦ GI symptoms: abdominal pain, diarrhoea
	  ◦ CNS: headache, confusion, coma
	  ◦ **Hyponatraemia, deranged LFTS**
	• Diagnosis: Legionella urine antigen/culture.
	Treatment: fluoroquinolone for 2-3wks or clarithromycin

H. Influenza	• Common in COPD, smokers • *Most common bacterial cause of acute exacerbation of COPD* • Most common organisms isolated from patients with bronchiectasis:
Pneumocystis jirovecii	• Most common opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS) • Occurs when CD4+ cell count < 200/mm3

Tuberculosis

- Chronic granulomatous disease caused by mycobacterium (acid-fast bacilli)
- In the pulmonary form, it is spread by inhalation of droplets containing the organism Mycobacterium tuberculosis (also referred to as the tubercle bacillus).
- In the nonpulmonary form, it is most often caused by the ingestion of infected milk

Primary Tuberculosis

- *Ghon complex is characteristic only of primary tuberculosis.*
    - Bacilli inhaled and lodged in alveoli Bacilli then initiate recruitment of macrophages and lymphocytes Macrophages undergo transformation into Epitheloid and Langerhans cellWhich aggregate with lymphocytes to form granuloma
    - *Aggregation of numerous granulomas Ghon focus*
    - *Ghon focus + lymph node involvement Ghon complex*
- *The granuloma of tuberculosis is referred to as a tubercle and is characterized by* ***central caseous necrosis*** *(Hallmark of disease)*

Secondary Tuberculosis

- Usually results from activation of a prior Ghon complex, with spread to a new pulmonary or extra pulmonary site
- Clinical characteristics include progressive disability, fever, hemoptysis, pleural effusion (often bloody), and generalized wasting

Pathologic Changes

- *Localized lesions, usually in the apical or posterior segments of the upper lobes.* Involvement of hilar lymph nodes is also common.
- Tubercle formation:
    - The lesions frequently rupture into the bronchi.
    - The caseous contents may liquefy and be expelled, resulting in cavitary lesions.
    - *Cavitation is a characteristic of secondary, but not primary, tuberculosis.*

Spread of Disease:

- Miliary tuberculosis: dissemination of tubercle bacilli via blood stream

Extrapulmonary disease feature

Lymph nodes	• Most common extra-pulmonary site • Most common site= cervical and mediastinal nodes • *Painless lymphadenopathy* • *Initially mobile, later becomes matted and suppurative*
Gastrointestinal disease	• *Most common site = Ileocecal region* • Right iliac fossa Mass • *Tuberculous peritonitis= abdominal pain, distention, ascitic fluid exudative with predominance of lymphocytes*
Gastrointestinal disease	• *Most common site = Ileocecal region* • Right iliac fossa Mass • *Tuberculous peritonitis= abdominal pain, distention, ascitic fluid exudative with predominance of lymphocytes*
Pericardial disease	• *Pericardial effusion= raised JVP, increased pericardial dullness* • *Constrictive pericarditis = raised JVP, Early third heart sound*
CNS	• Meningitis • Tuberculoma

Bone and joint disease	• Bone:
	  • *Most common site is spine known as Pott's disease*
	  • *Most common site of spine= Lower thoracic and lumber region*
	  • *Psoas abscess = Cold abscess in inguinal region*
	• Joints:
	  • *Most common site= Hip and Knee*

MDR and XDR-TB

MDR-TB (Multi-Drug Resistant TB)	• TB which is resistant to isoniazid and rifampicin
XDR-TB (Extensive Drug Resistant TB)	

PPD/Mantoux skin tests/tuberculin skin test.

- 0.1 mL of purified protein derivative (PPD) is injected intradermally on the volar surface (portion of the forearm that is on the same side as the palm)
- The transverse width in millimeters of induration (not erythema) at the skin test site is measured after 48-72 hrs.
- PPD test only useful in latent Tb (asymptomatic patients) and not to be used in symptomatic patients or those with abnormal CXR
- **Interpretation:**

Induration of >15mm	• Considered positive in persons with no risk factors for TB
Induration of >10mm	• Considered positive in • Prisoners • Health care workers • *Persons working in Nursing homes, Homeless shelters & other health care facilities* • Persons with following medical conditions (DM, Leukaemia, Lymphoma, CKD, CA head & Neck) • IV drug users
Induration of >5mm	• Considered positive in • Recent contacts of individuals with active tuberculosis. • *HIV positive patients* • Immunocompromised patient (e.g. Prednisolone 15mg/day for 1 month or more) • Persons with fibrotic changes on chest films suggestive of prior tuberculosis. • Patients with organ transplants
False negative result	• Severe TB • New-born and elderly • HIV if CD4 count < 200 • *Malnutrition* • Malignancy

TB Treatment and drugs adverse effects

Drug	Dosage	DOTS (Directly observe therapy short-course)	Complications
		Initially daily therapy for 2 weeks followed by drugs 3 times/week	
Isoniazid	5 mg/kg	15 mg/kg	*Peripheral neuropathy, Hepatitis*
Rifampicin	10 mg/kg	10mg/kg	*Orange-red colour body secretions (urine, tears), hepatitis,*
Ethambutol	15-25mg/kg	25-30mg/kg	*Optic neuritis (colour blindness for green, decreased visual acuity)*
Pyrazinamide	15-30 mg/kg	50-70 mg/kg	*Hyperuricemia, Gout, Hepatitis*
Streptomycin	15mg/kg	25-30mg/kg	*8^{th} (vestibular) nerve damage, nephrotoxicity.*

Treatment: (Duration 6 months)

- Initial therapy ---(2 months---4 drugs)
    - Mnemonic **RIPE** : (**R**ifampicin, **I**soniazid, **P**yrazinamide, **E**thambutol)
    - ***Pyridoxine (vitamin B6) should be used with INH to prevent neuropathy.***
- Continuation phase –(4 months—2 drugs)----That are Isoniazid & Rifampicin
- Extended treatment: (For 9-12 months)—considered in the following
    - HIV- positive patients, Tuberculous osteomyelitis, Miliary TB, Meningitis, Pregnancy
    - *Pyrazinamide is contraindicated in pregnancy*

    Baby can be breastfeed while taking ATT

Pleural Effusions

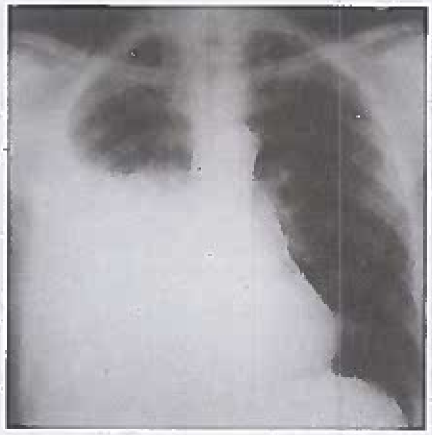
- Excess accumulation of fluid between pleural layers
- Restricted lung expansion during inspiration.
- Can be treated with thoracentesis to remove fluid

Induration of >10mm	Exudative Effusion
• Alteration of systemic factors that affect the formation and absorption of pleural fluid (e.g., Increased capillary hydrostatic pressure, decreased plasma oncotic pressure)	• Increased permeability of pleural capillaries or lymphatic dysfunction
• Usually bilateral	• Can be bilateral or unilateral
• ↓*protein content*	• ↑*protein content*
• Causes ◦ Mnemonic: **S**ome **P**ersistent **P**eople **C**an ◦ **C**ause **N**ausea ▪ **S**VC syndrome ▪ **P**eritoneal dialysis ▪ **P**ulmonary embolism ▪ **C**HF (>90% cases—most common) ▪ **C**irrhosis ▪ **N**ephrotic syndrome	• Causes ◦ Mnemonic: **PICTURE MAP** ▪ **P**arapneumonic effusion (associated with bacterial pneumonia, lung abscess) ▪ **I**nfections (viral, bacterial, fungal) ▪ **C**ancer ▪ **T**rauma/tumour (chylothorax) ▪ **U**remia ▪ **R**ickettsial infection ▪ **E**sophageal perforation ▪ **M**eigs syndrome (ascites +hydrothorax associated with ovarian tumor) ▪ **A**sbestos ▪ **P**ancreatic disease (elevated pleural fluid amylase)

Distinguish clinically using Light's Criteria

Lights Criteria	Transudate	Exudate
Pleural fluid protein: serum protein	<0.5	*>0.5*
Pleural fluid LDH: to serum LDH	<0.6	>0.6
Pleural LDH	<2/3 upper limit of N serum LDH	>2/3 upper limit of N serum LDH

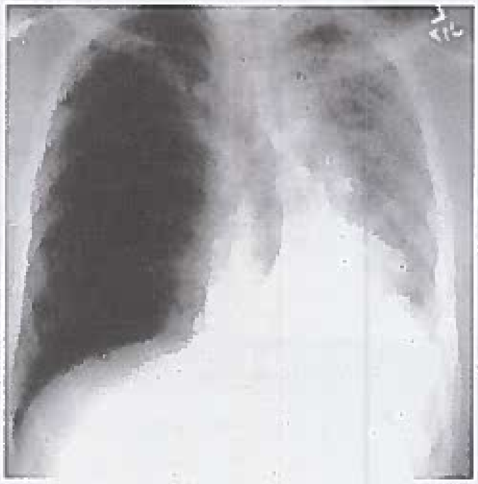
Note:
All criteria for transudate must be fulfilled to be considered a transudative effusion.
If any one of the criteria for exudates is met – it is an exudate



Pneumothorax

- Accumulation of air in pleural space
- *Unilateral chest pain* and dyspnea, unilateral chest expansion
- ↓*tactile fremitus (only increased in consolidation e.g. pneumonia)*, hyper resonance
- Diminished breath sounds, all on the affected side.

Primary Spontaneous	• Due to rupture of apical blebs or cysts. Occurs most frequently in tall, thin, young males.
Secondary Spontaneous	• Due to diseased lung (e.g., bullae in emphysema, infections), mechanical ventilation with use of high pressures→barotrauma.
Traumatic Pneumothorax	• Caused by blunt (e.g. rib fracture) or penetrating (e.g., gunshot) trauma
Tension Pneumothorax	• Can be any of the above. • **Air enters pleural space but cannot exit.** • Increasing trapped air→tension pneumothorax. • *Trachea deviates away from affected lung*



Lung Abscess

- Localized collection of pus within parenchyma
- Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [e.g., alcoholics, epileptics]) or bronchial obstruction (e.g., cancer).
- *Due to anaerobes (e.g., Bacteroides, Fusobacterium, Peptostreptococcus) or* ***S. aureus.***
- **Air-fluid levels often seen on CXR.**

Sleep Apnea

- Repeated cessation of breathing > 10 seconds during sleep but Normal PaO_2 during the day.

Obstructive sleep apnea	• Respiratory effort against airway obstruction. Associated with obesity, loud snoring. Caused by: Adults: excess parapharyngeal tissue Children: adenotonsillar hypertrophy • Treatment: weight loss, CPAP, surgery.
Central sleep apnea	• No respiratory effort (due to CNS injury/toxicity).

Lung Cancers

- Leading cause of cancer death.

Risk Factors	• *Smoking,* passive smoke, radon, asbestos, family history. *Genetic: Epidermal Growth Factor Receptor gene (EGFR) mutations often identified in non-small cell carcinomas (chiefly adenocarcinomas) in never-smokers*
Presentation	• Cough, hemoptysis, bronchial obstruction, and wheezing. • *Pneumonic "coin" lesion on CXR or noncalcified nodule on CT*
Sites Of Metastases	• From Lung Cancer To Other Sites: · *Adrenals, brain, bone (pathologic fracture), liver (jaundice, hepatomegaly).* • To The Lung From Other Sites: · Most often from breast, colon, prostate, and bladder cancer
Complications	• Superior Vena Cava Syndrome · *Compression or invasion of the superior vena cava, resulting in facial swelling and cyanosis along with dilation of the veins of the head, neck, and upper extremities* • Pancoast tumor (Superior Sulcus tumor): · *Involvement of the apex of the lung, often with Horner syndrome (Ipsilateral ptosis, miosis, and anhidrosis), due to involvement of the cervical sympathetic plexus. Also causes SVC syndrome, hoarseness (Recurrent Laryngeal Nerve Compression)* • Paraneoplastic Endocrine Syndromes: · Small cell carcinoma: ▪ *Adrenocorticotropic hormone (ACTH) or ACTH-like activity* ▪ *Syndrome of inappropriate antidiuretic hormone secretion (SIADH)* ▪ *Lambert-Eaton myasthenic syndrome: Antibodies against presynaptic Ca2+ channels* · Squamous cell carcinoma: ▪ *PTH-hormone-like activity (hypercalcemia)*

Classification

Small cell (oat cell) carcinoma	Central	• *Neoplasm of neuroendocrine Kulchitsky cellssmall dark blue cells* • *Amplification of myc oncogenes common.* • Prone to early hematogenous spread. It is rarely amenable to surgical resection and has a very aggressive course with a median survival (untreated) of 6- 1 8 weeks • Treat with chemotherapy.
Adenocarcinoma	Peripheral	• *Most common lung cancer in non-smokers and overall (except for metastases)* • Glandular pattern on histology • **Associated with EGFR, amenable to EGFR tyrosine kinase inhibitors**

Squamous cell carcinoma	Central	• *Most common in smokers*
Large cell carcinoma	Peripheral	• Highly anaplastic undifferentiated tumor • Poor prognosis. • Pleomorphic giant cells. • *Can secrete β-hCG*
Bronchial carcinoid tumor		• Excellent prognosis

Note: **S**quamous and **S**mall cell carcinomas are **S**entral (central).

Chapter 5: Renal

Nephrotic syndrome

- Includes a group of conditions characterized by increased basement membrane permeability
- Characteristic features:
  - *Massive proteinuria (daily loss of ≥ 3.5 grams of protein per day).*
  - Hypoalbuminemia (serum albumin less than 3 g/100 mL)
  - Generalized edema.
  - Hyperlipidemia and hypercholesterolemia are caused by increased hepatic lipoprotein synthesis.
- Causes:
  - **Primary glomerular disease:** Minimal change disease, Membranous GN, Focal segmental glomerolosclerosis
  - **Systemic diseases:** SLE, Amyloidosis, Diabetic nephropathy

Minimal change disease (lipoid Nephrosis)	• *Most common cause of Nephrotic syndrome in children* • Light microscopy→normal-appearing glomeruli. • Electron microscopy→*disappearance or fusing of epithelial foot processes.* • *Excellent response to corticosteroids* • Associations: · Hodgkin's lymphoma, thymoma, infectious mononucleosis

Membranous nephropathy (membranous glomerulonephritis	• *Most common cause of Nephrotic syndrome in adults*
	• Light microscopy→diffuse capillary and GBM thickening
	• Electron microscopy→*spike and dome" appearance with Subepithelial deposits.*
	• Poor response to corticosteroids
	• Associations:
	  · ***SLE (10%), hepatitis B**, syphilis, malaria infection; drugs (gold salts or penicillamine); or **malignancy.***
	  · *The disorder sometimes causes renal vein thrombosis, because of loss of antithrombin III, protein C and S &↑ fibrinogen*

Focal segmental glomerolosclerosis	• It is more common in African Americans and is ***associated with HIV.*** • It is characterized by sclerosis of some glomeruli, in these affected glomeruli only a portion of capillary tuft is involved • Light Microscopy→segmental sclerosis • Electron Microscopy→*effacement of foot process/Podocyte effusion* (same as Minimal change disease, but minimal change > focal segmental sclerosis)

Diabetic nephropathy	• ↑*in mesangial matrix* two patterns:
	  · Diffuse glomerulosclerosis→diffusely increase in mesangial matrix.
	  · Nodular glomerulosclerosis→*nodular accumulations of mesangial matrix material (**Kimmelstiel-Wilson nodules**).*
	• Electron microscopy→↑*in thickness of the glomerular basement membrane*

Renal Amyloidosis	• Amyloidosis refers to accumulation of insoluble fibrillar proteins that form β-pleated sheaths, two types • Light Microscopy—*Congo red stain shows apple-green birefringence*

Primary ( ) amyloidosis	Secondary ( ) amyloidosis
Most common→in developed world.	Less common in developed countries
Due to deposition of proteins from Ig Light chains	Occurs in patients with long-standing neoplasia or inflammation and is associated with *serum amyloid protein called AA protein*
Can occur as a plasma cell disorder or associated with multiple myeloma and Waldenström macroglobulinemia	*It is often seen in concert with tuberculosis, leprosy, RA*

Nephritic syndrome

- (NephrItic) Inflammatory rupture of the glomerular capillaries, with resultant bleeding
- Characterized features: (**A HOPE**)
    - **A**zotemia
    - *Hematuria*
    - **H**ypertension
    - **O**liguria
    - *Proteinuria (less than 3g/day)*
    - **E**dema

Acute post streptococcal glomerulonephritis	• Most common type of post-infectious glomerulonephritis in childrens
	• *Occurs 1-4 weeks after a sore throat caused by group A β-hemolytic streptococci i.e. streptococcus pyogenes*
	• *Type III hypersensitivity reaction.*
	• Clinical features:
	  ◦ Sudden onset of fever, oliguria, *hematuria (cocoa-colored urine)*
	• Findings:
	  ◦ *Serum C3 decreased*
	  ◦ *ASO titers elevated*
	  ◦ Light microscopy→glomeruli enlarged and hypercellular
	  ◦ Electron microscopy→*Subepithelial humps*
	  ◦ Immunofluorescence→lumpy bumpy appearance

Rapidly progressive (crescentic) glomerulonephritis	• Nephritic syndrome that progresses rapidly to renal failure within weeks or months • Light microscopy & Immunofluorescence *Crescent shape glomerulonephritis* • Disease processes that may result in this pattern are

Goodpasture syndrome	Wegener's glomerulonephritis
• *Type II hypersensitivity reaction caused by antibodies against GBM and alveolar basement membrane* • ***IgG deposits on renal biopsy***	• *It is necrotizing medium sized small vessel vasculitis*
• *Involves lung and renal vessels*	• *Involving upper respiratory tract, lung and renal vessels*
• *Hemorrhagic pneumonitis (pneumonia plus hemoptysis) Nephritic syndrome*	• *Sinusitis, otitis media* • *Hemorrhagic pneumonitis (pneumonia plus hemoptysis)* • *Nephritic syndrome*

IgA nephropathy (Berger disease)	• *Most common type of nephritic syndrome overall and is due to deposition of IgA in the mesangium* • *It presents with recurrent episodes of hematuria following upper RTI, GI infections, occurs 1-2 days after infection* • Associations: *coeliac disease/dermatitis herpetiformis,* ***Henoch-Schonlein purpura*** • Light microscopy→mesangial expansion • Immunofluorescence→granular mesangial IgA and lambda light chain deposition • *Not to be confused with Buerger disease (Thromboangiitis obliterans).*
Alport syndrome	• ***Mvost commonly X-linked dominant.*** *Defective glomerular basement membrane synthesis due to abnormal collagen type IV* Clinical features: Mnemonic: **"can't see, can't pee, and can't hear a bee."** · Eye problems (e.g., retinopathy, lens dislocation) · Glomerulonephritis · Sensorineural deafness • Electron microscopy→ *"Basket-weave" appearance.*

Nephritic-Nephrotic syndrome

- Severe nephritic syndrome with profound GBM damage that damages the glomerular filtration charge barrier →nephrotic-range proteinuria (> 3.5g/day) and concomitant features of nephrotic syndrome. Can occur with any form of nephritic syndrome, but is most commonly seen with:
  - Membranoproliferative glomerulonephritis (MPGN) (also known as messangiocapillary glomerulonephritis)
    - MPGN is a nephritic syndrome that often co-presents with nephrotic syndrome

	Type I MPGN "Subendothelial Immune Complex"	Type II MPGN "Dense Deposit Disease"
Cause	• Immune complex nephritis	• Also known as dense deposit disease, associated with C3 nephritic factor
Mechanism	• It results from activation of both classic and alternate complement pathway	• It results from activation of only alternate complement pathway C3 nephritic factor, which is an auto-antibody that prevents degradation of C3- convertase causing sustained activation of C3, resulting in very low C3 levels
Causes	• May be 2° to hepatitis B or C infection. Idiopathic cryoglobulinaemia	• Partial lipodystrophy Factor H deficiency
H&E stain	• Tram track appearance	• Tram track appearance
EM	• *Subendothelial deposits*	• Intramembranous deposits

Quick review and some extra points

- *IgA nephropathy= Mesangial deposits in glomerular basement membrane*
- *IgM and C3 deposits in= FSGS (focal segmental glomeroloscelorosis)—associated with HIV*
- *Linear deposits= Goodpasture syndrome*
- *Subepithelial deposits/humps= post streptococcal GN*
- *Subendothelial deposits = SLE and Membranoproliferative glomerulonephritis (MPGN) type-1*
- *Spike and Dome are seen in = Membranous glomerulonephritis – (associated with SLE, Hep B)*
- *Selective proteinuria= Minimal change disease*

  Alport syndrome= "Basket-weave" appearance

Post streptococcal glomerulonephritis Vs. IgA nephropathy

Post Streptococcal Glomerulonephritis	IgA nephropathy
• Occurs 1-2 weeks after infection	• Occurs 1-2 days after infection
• C3 levels low	• C3 levels normal

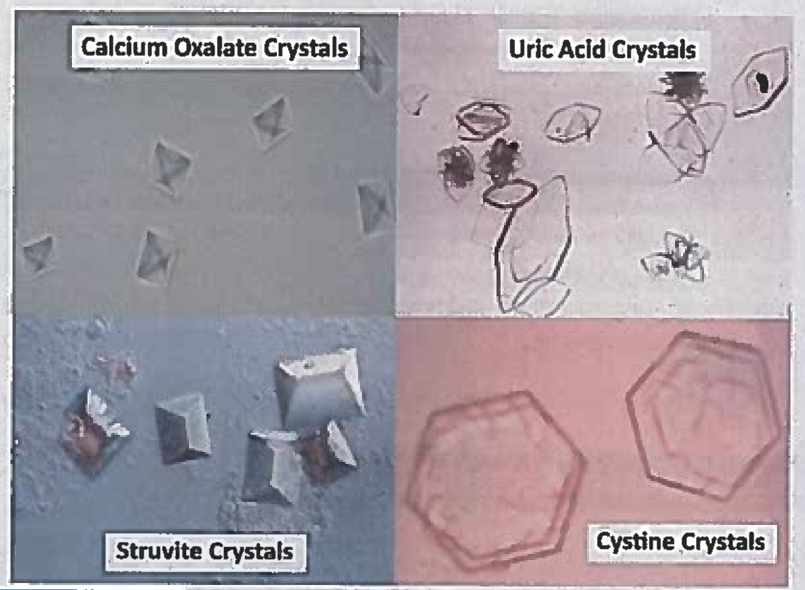
SLE Renal Complications

- WHO classification
    - Class I: normal kidney
    - Class II: mesangial glomerulonephritis
    - Class III: focal (and segmental) proliferative glomerulonephritis
    - ***Class IV: diffuse proliferative glomerulonephritis--- most common and severe form.***
    - Class V: diffuse membranous glomerulonephritis
    - Class VI: sclerosing glomerulonephritis

Kidney Stones

- Features→flank pain (which is colicky, radiating to groin), hematuria
- Complications→pyelonephritis, hydronephrosis
- Types

Calcium stones	Ammonium magnesium phosphate (Also known as struvite)	Uric acid	Cystine
• Most common (80%) • Calcium oxalate more common than calcium phosphate stones.	• 2nd common (15%) of stones.	• About 5% of all stones.	• Less common
• Caused by: · Ethylene glycol (antifreeze) ingestion · Vitamin C abuse · Hypercalcemia which may be caused by hyperparathyroidism malignancy, sarcoidosis, vitamin D intoxication, and the milk-alkali syndrome.	• Caused by: · Urease ⊕ bugs (e.g., **Proteus Staphylococcus saprophyticus, Klebsiella**) that hydrolyze urea to ammonia→urine alkalinization. • *Commonly form staghorn calculi*	• Caused by: · Strong association with Hyperuricemia (e.g., gout) • Often seen in leukemia.	• Caused by: · Cystine-reabsorbing PCT transporter loses function, causing cystinuria. Results in poor reabsorption of Ornithine, Lysine, Arginine (**COLA**). • Can form staghorn calculi.
• Envelop shaped	• Coffin lid	• Rhomboid or rosettes	• Hexagonal shape
• Radiopaque	• Radiopaque	• *RadiolUcent*	• Radiolucent
• Treatment: · Low-sodium diet · Thiazides · Citrate	• Treatment: · Eradication of underlying infection · Surgical removal of stone	• Treatment: · Alkalinization of urine · Allopurinol	• Treatment: · Alkalinization of urine · Low sodium diet · Chelating agents if refractory.



Renal Cyst Disorders

Autosomal Dominant Polycystic Kidney Disease

- Numerous cysts in cortex and medulla causing bilateral enlarged kidneys ultimately destroy kidney parenchyma.
- *Autosomal dominant; in which renal parenchyma is replaced by cyst*
- Manifests between 15 and 30 years of age, even though the genetic defect is present at birth.
- The disease occurs bilaterally; the kidneys are greatly enlarged.
- Clinical features:
  - Presents with flank pain, hematuria, hypertension, urinary infection, progressive renal failure (50% of individuals).
- Types:

ADPKD Type 1	ADPKD Type 2
• 85% of cases	• 15% of cases
• Mutation in PKD1 (which code for polycystin-1)	• Mutation in PKD2 (which code for polycystin-2)
• **Chromosome 16**	• **Chromosome 4**

- Ultrasound diagnostic criteria (in patients with positive family history)
  - Two cysts, unilateral or bilateral, if aged < 30 years
  - Two cysts in both kidneys if aged 30-59 years
  - Four cysts in both kidneys if aged > 60 years
- Features
  - Hypertension, recurrent UTIs, abdominal pain, renal stones, chronic kidney disease
- Extra-renal manifestations
  - Liver cysts (70%), ***Berry aneurysms of the circle of Willis*** (8%)
  - Cardiovascular system: MVP, *aortic dilation and dissection*
- Treatment: ACE inhibitors or ARBs.

Autosomal Recessive Polycystic Kidney Disease

- Cystic dilation of collecting ducts.
- **Often presents in infancy**.
- Associated with
  - Congenital hepatic fibrosis.
  - Significant oliguric renal failure in utero can lead to **Potter sequence**.
- Death from this autosomal recessive disorder results shortly after birth.

Medullary Cystic Disease	• Inherited disease causing tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. • Medullary cysts usually not visualized; shrunken kidneys on ultrasound. • Poor prognosis
Simple Vs Complex Renal Cysts	**Simple Renal Cysts**: • Filled with ultrafiltrate • Very common • Found incidentally and typically asymptomatic. **Complex Renal Cysts**: • Solid components on imaging • Less common comparitevly • Require follow-up or removal due to risk of renal cell carcinoma

Simple Renal Cysts	Complex Renal Cysts
• Filled with ultrafiltrate	• Solid components on imaging
• Very common	• Less common comparitevly
• Found incidentally and typically asymptomatic.	• Require follow-up or removal due to risk of renal cell carcinoma

Urinary Tract Infection (Acute Bacterial Cystitis)

Definition	• Inflammation of urinary bladder. usually defined as more than 10^5 organisms per milliliter of mid-urine sample
Clinical features	• Presents as suprapubic pain, dysuria, urinary frequency, urgency, Pyuria (↑neutrophils)
Risk factors	• Female gender (short urethra), sexual intercourse ("honeymoon cystitis"), indwelling catheter, diabetes mellitus, impaired bladder emptying
Causes	• *E coli (most common).* • *Staphylococcus saprophyticus—seen in sexually active young women* (E coli is still more common in this group). • Klebsiella. • Proteus mirabilis—urine has ammonia scent.

Pyelonephritis

Acute Pyelonephritis	• Neutrophils infiltrate renal interstitium. Affects cortex with relative sparing of glomeruli/vessels. Clinical features;
	  ◦ Fever, flank pain, nausea/vomiting, chills.
	• Causes includes
	  ◦ Ascending UTI (E. coli is most common)
	• Risk factors:
	  ◦ Diabetes mellitus, pregnancy, indwelling urinary catheter, urinary tract obstruction
	• Complications:
	  ◦ Chronic pyelonephritis, renal papillary necrosis, perinephric abscess, urosepsis.
	• Treatment: Antibiotics.

Chronic Pyelonephritis	• Coarse, asymmetric corticomedullary scarring, blunted calyx.
	• Atrophic tubules can contain eosinophilic casts resembling thyroid tissue **(thyroidization of kidney)**
	• Causes:
	  ◦ Chronic urinary tract obstruction and repeated bouts of acute inflammation.
	• Complications:
	  ◦ Renal hypertension and end-stage renal disease.
	• **Xanthogranulomatous pyelonephritis**
	  ◦ Rare
	  ◦ Grossly orange nodules that can mimic tumor nodules
	  ◦ Characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages.

Renal Tubular Acidosis

- *A disorder of the renal tubules that leads to **normal anion gap (hyperchloremic) metabolic acidosis***

	Distal renal tubular acidosis (type 1)	Proximal renal tubular acidosis (type 2)	Hyperkalemic renal tubular acidosis (type 4)
Defect	Defect in ability of α intercalated cells to secrete H+→no new HCO3	*Defect in PCT HCO3 reabsorption*	↓aldosterone productionhyperkalemia ↓NH3 synthesis in PCT↓NH4+ excretion
Urine pH	> 5,5	< 5.5.	< 5.5.
Serum K+	*Hypokalemia*	*Hypokalemia*	*Hypokalemia*
Causes	Amphotericin B toxicity congenital anomalies (obstruction) of urinary tract	**Fanconi syndrome** and carbonic anhydrase inhibitors	Diabetes, ACE inhibitors, ARBs, NSAIDs

Acute Kidney Injury (Acute Renal Failure)

- Acute and reversible deterioration of renal function which develops over periods of days to weeks and measure by↑creatinine and↑BUN or by oliguria/anuria.
- Causes

Pre- renal causes of ARF	• Heart failure • Blood loss • Fluid loss • Renal artery stenosis or occlusion
Intrinsic renal causes of ARF	• Acute tubular necrosis Interstitial disease ◦ Characterized by antibodies and eosinophils attacking cells lining the tubules • Primary and secondary glomerulonephritis
Post- renal causes of ARF	• Obstruction because of ◦ Stones ◦ Tumors ◦ Inflammation ◦ Prostate enlargement

Comparison between Prenal, Intrinsic And Post Renal Causes Of ARF

- **Prerenal casues------in this kidneys hold on to sodium to preserve volume**

	Pre-Renal	Intrinsic	Post-Renal
Urine osmolality (mOsm/kg)	> 500	< 350	< 350
Urine Na+ (mEq/L)	< 20	> 40	> 40
FE_{Na}+ (mEq/L)	< 1%	> 2%	< 1% (mild) > 2% (severe)
Serum BUN/Cr	> 20	< 15	Varies

Consequences of Renal Failure (MAD HUNGER)

- Inability to make urine and excrete nitrogenous wastes.
    - **M**etabolic **A**cidosis
    - **D**yslipidemia (especially ↑triglycerides)
    - **H**yperkalemia, **H**ypocalcemia (↓active form of vitamin D)
    - **U**remia—clinical syndrome marked by ↑BUN (Nausea, anorexia, encephalopathy)
    - **N**a+/H2O retention (HF, pulmonary edema, hypertension)
    - **G**rowth retardation and developmental delay
    - **E**rythropoietin failure (anemia)
    - **R**enal osteodystrophy

Tubular and Interstitial Disorders of the Kidney

Disorder	Notes

Acute interstitial nephritis (tubulointerstitial nephritis)	• Acute interstitial renal inflammation.
	• Pyuria (classically eosinophils) and azotemia occurring after administration of drugs
	• Causes: (Mnemonic: Remember these **P'S**)
	  ◦ **P**ee (diuretics)
	  ◦ **P**ain-free (NSAIDs)
	  ◦ **P**enicillins and cephalosporins
	  ◦ **P**roton pump inhibitors
	  ◦ Rifam**P**in
	  ◦ Other **P**rocesses such as autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis)
	• The nephritis resolves on cessation of exposure to the inciting drug.

Renal papillary necrosis (necrotizing papillitis)	• Ischemic necrosis of the tips of the renal papillae gross hematuria and proteinuria.
	• May be triggered by recent infection or immune stimulus.
	• Associated with: (Mnemonic: **SAAD** papa with **papillary** necrosis)
	  ◦ **S**ickle cell disease or trait
	  ◦ **A**cute pyelonephritis
	  ◦ **A**nalgesics (NSAIDs)
	  ◦ **D**iabetes mellitus

Acute tubular necrosis	• Is the most common cause of acute renal failure and most common cause of acute kidney injury in hospitalized patients • This condition is reversible but if left untreated can be fatal, especially during initial oliguric phase. • Key finding: granular ("muddy brown") casts • Can be caused by ischemic or nephrotoxic injury

Ischemic Injury	Nephrotoxic Injury
Secondary to ↓renal blood flow	Secondary to injury resulting from toxic substances.
Examples: • Hypotension, shock, sepsis, hemorrhage, HF	Examples: • Aminoglycosides, radiocontrast agents, lead, cisplatin, crush injury (myoglobinuria), ethylene glycol, hemoglobinuria
PCT and thick ascending limb are highly susceptible to injury	PCT is particularly susceptible to injury.

Hydronephrosis

Definition	• Progressive dilation of the renal pelvis and calyces
Causes	• Urinary tract obstruction (eg, renal stones, severe BPH, cervical cancer) • Retroperitoneal fibrosis • Vesicoureteral reflux
Findings	• Dilation occurs proximal to site of pathology. • Serum creatinine becomes elevated if obstruction is bilateral or if patient has only one kidney. • Leads to compression and possible atrophy of renal cortex and medulla
Treatment	• Hydronephrosis can be physiologic • Treatment should be guided at improving symptoms, treating infections, or improving renal function • Urgent treatment may require percutaneous nephrostomy tube or ureteral stenting to relieve pressure

Disorders of Renal Tubular Function

Fanconi syndrome	• This manifestation of generalized dysfunction of the proximal renal tubules may be hereditary or acquired.
	• Impaired reabsorption of glucose (glycosuria), amino acids (aminoaciduria), phosphate (hypophosphatemia), and bicarbonate (systemic acidosis) is characteristic.
	• Causes:
	  ◦ Hereditary defects (eg, Wilson disease, glycogen storage disease),
	  ◦ Ischemia
	  ◦ Multiple myeloma
	  ◦ Nephrotoxins/drugs (eg, cisplatin, tenofovir), lead poisoning

Hartnup disease	• *This impaired tubular reabsorption of tryptophan is genetically determined.* • *This condition leads to pellagra-like manifestations.*
Bartter's syndrome, Gitelman's syndrome, Liddle's syndrome	(see table below)

Bartter's syndrome	Gitelman's syndrome	Liddle's syndrome
• Autosomal recessive	• Autosomal recessive	• Autosomal dominant
• It is due to defective chloride absorption at the **Na+ K+ 2Cl- cotransporter in the ascending loop of Henle** (like furosemide—think of this disease as like taking large doses of furosemide)	• Is due to a **defect in the thiazide-sensitive Na+ Cl- transporter in the distal convoluted tubule.**	• **Disordered sodium channels in the distal tubules** leading to increased reabsorption of sodium. (similar to hyperaldosteronism)
• **Normotension + severe hypokalaemia**	• **Normotension + Hypokalaemia + Hypomagnesaemia**	• **Hypertension + Hypokalaemia**

Quick Summary

Condition	Blood Pressure	Plasma Renin	Aldosterone	Serum Mg++	Urine Ca++
SIADH	Normal/↑	↓	↓		
Primary Hyperaldosteronism	↑	↓	↑		

Renin-secreting tumor	↑	↑	↑		
Bartter syndrome	Normal	↑	↑		↑
Gitelman syndrome	Normal	↑	↑	↓	↓
Liddle syndrome	↑	↓	↓		

Chronic Kidney Disease (CKD)

Definition

- Impaired renal function for >3 months based on abnormal structure or function

  OR
- GFR <60mL/min for >3 months with or without evidence of kidney damage

Causes

- Inherited causes:
  - Adult polycystic kidney disease –most common
  - Alport's syndrome
  - Fabry's disease
- Acquired casues:
  - DM Type II >> Type I----Most common
  - Hypertension or renovascular disease
  - Pyelonephritis
  - Glomerulonephritis (commonly IgA nephropathy, systemic disorders, eg SLE, vasculitis)
  - Unknown: up to 20% in the UK have no obvious cause of CKD.

Classification

Stage	GFR (mL/min)	Notes
1	>90	Normal or GFR with other evidence of renal damage
2	60-89	Slight↓GFR with other evidence of renal damage
3A 3B	45-59 30-44	Moderate↓GFR with or without evidence of other renal damage
4	15-29	Sever↓GFR with or without evidence of renal damage
5	<15	Established renal failure

Labs

- Hb (normochromic, normocytic anaemia), ESR, U&E, glucose (DM).
- ↓Ca2+, ↑PO_4^{3-}, ↑alk phos (renal osteodystrophy).
- ↑PTH if CKD stage 3 or more

Treatment

- **Limiting progression/complications**
  - **BP**
    - *Target BP is <130/80 (<125/75 if diabetic or ACR >70).*
    - *Drug of choice--- ACE-inhibitors or ARB.*
- **Renal bone disease** (risk of osteodystrophy or adynamic bone disease):
    - Check PTH and treat if raised.
    - *PO_4^{3-} rises in CKD, which↑PTH further.*
    - Restrict diet, give binders to↓gut absorption.
    - Vit D analogues (eg alfacalcidol) and Ca2+ supplements↓bone disease
    - and hyperparathyroidism
  - **Cardiovascular:**
    - *Most common cause of death*

      Give statins & aspirin also (CKD is not a contraindication to the use of low-dose aspirin, but beware of risk of bleeding).

- **Diet:**
  - Moderate protein diet, K+ restriction if hyperkalaemic, and avoidance of high phosphate foods (eg milk, cheese, eggs).
- **Symptom control**
  - **Anaemia:**
    - Replace iron/B12/folate if necessary.
      If still anaemic consider recombinant human erythropoietin. There are many formulations
  - **Acidosis:**
    - Sodium bicarbonate supplements for patients with low serum level
  - **Oedema:**
    - High doses of loop diuretics may be needed
      Restriction on fluid and sodium intake.

Tumors of the Kidney, Urinary Tract, and Bladder

Renal cell carcinoma

Originate	• **Symptom control**
Incidence	• Most common renal malignancy and most common in men 50–70 years**symptom control**
Associated with	• *Gene deletion on chromosome* ***3*** ***(RCC=3*** *letters= Chromosome* ***3)***
Presenting features	• Flank pain, palpable mass, and hematuria, fever, *Secondary polycythemia* • Associated with paraneoplastic syndromes (eg: ectopic EPO, ACTH, PTHrP, renin).
Invades	• Renal vein (may develop varicocele if left sided) then IVC and spreads hematogenously
Metastasizes to	• Lung and bone

Nephroblastoma (Wilms Tumor)

Originate	• From primitive metanephric tissue
Incidence	• *Most common renal malignancy of early childhood.* *Incidence peaks in children 2 to 4 years of age.*
Associated with	• Mutations of tumor suppressor genes WT1 or WT2 on chromosome 11.
Presenting features	• Presents with large, palpable, unilateral flank mass and/or hematuria
Part of several syndromes	• **WAGR complex** ◦ **W**ilms tumor, **A**niridia (absence of iris), **G**enitourinary malformations, mental **R**etardation/intellectual disability ◦ Associated with deletion *WT-1* tumor suppressor gene • Denys-Drash: ◦ Wilms tumor, early-onset nephrotic syndrome, male pseudohermaphroditism ◦ Associated with abnormalities of WT1 gene. • Beckwith-Wiedemann: ◦ Wilms tumor, macroglossia, organomegaly, hemihyperplasia Associated with mutation of WT2 gene.

Transitional Cell Carcinoma

- Most common tumor of urinary tract system
- Can occur in renal calyces, renal pelvis, ureters, and bladder.
- Can be suggested by *painless hematuria* (no casts).
- Associated with problems in your **P**ee **SAC**:
    - **P**henacetin, ***S**moking*, **A**niline dyes, and **C**yclophosphamide.

Squamous Cell Carcinoma of the Bladder

- Chronic irritation of urinary bladder squamous metaplasia dysplasia and squamous cell carcinoma.
- Risk factors include ***Schistosoma haematobium*** (**S** for **S**quamous cell carcinoma= **S** for ***S**chistosoma haematobium*) infection, *smoking*, chronic nephrolithiasis.
- Presents with *painless hematuria.*

Causes of Sterile Pyuria

- Partially treated UTI
- Urethritis e.g., Chlamydia
- Renal tuberculosis
- Renal stones
- Appendicitis
- Bladder/renal cell cancer
- Adult polycystic kidney disease

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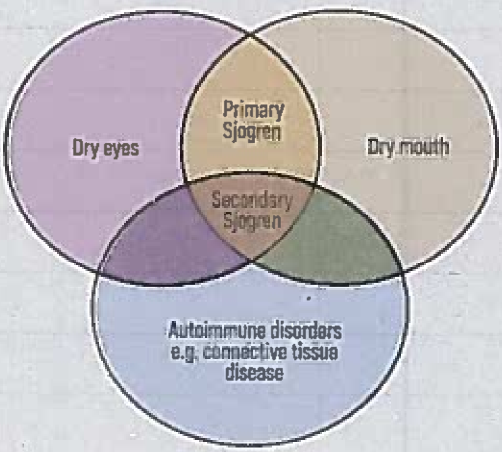
Chapter 6: Gastrointestinal Tract

Oral Cancer

- *Oral cancer is most frequently squamous cell carcinoma.*
- *Involvement of the tongue occurs in more than 50% of cases.*
- Carcinoma of the mouth, tongue, and esophagus is often associated with the combined abuse of tobacco and alcohol.
- Oral cancer may be associated with irritants such as pipe smoking, chewing tobacco, or betel nuts.
- *Unlike oropharyngeal carcinoma, it is not typically related to human papillomavirus infection.*

Diseases and Tumors of Salivary Glands

Sjögren syndrome.	• Autoimmune disorder. • Characteristics includes *Keratoconjunctivitis sicca (dry eyes)* *Xerostomia (dry mouth)* *Associated connective tissue disease, most often Rheumatoid arthritis.* • Sjögren syndrome is associated with an increased incidence of malignant lymphoma
Pleomorphic adenoma (mixed tumor)	• *Benign and most common salivary gland tumor* • It has been called *"mixed tumor"* because of the presence of myxoid and cartilage- like elements, as well as epithelial cells • *Presents as painless, mobile mass* • Often, the tumor is difficult to remove completely because of its proximity to the facial nerve, and it is likely to recur after resection
Warthin tumor (papillary cystadenoma lymphomatosum)	• Benign cystic tumor *frequently bilateral tumor* • *Most common in smokers.* • *The cyst fluid has a characteristic "motor oil" quality*
Mucoepidermoid carcinoma	• *Most common malignant tumor of the salivary glands.* Has mucinous and squamous components. Typically presents as painless, slow-growing mass.



Diseases and Tumors of Esophagus

Esophageal Varices	• Dilated submucosal veins in lower 1/3 of esophagus 2° to portal hypertension. • Common in alcoholics, may be source of upper GI bleeding.

Plummer-Vinson Syndrome	• Triad of ("Plumbers" DIE).
	  ◦ Dysphagia
	  ◦ Iron deficiency anemia, and
	  ◦ Esophageal webs.
	• Increased risk of esophageal squamous cell carcinoma

GERD	• Reflux of gastric contents into lower esophagus because of incompetent lower esophageal sphincter (*↓LES tone*) • Commonly presents as heartburn and regurgitation upon lying down. • Associated with excessive use of alcohol and tobacco, pregnancy, or scleroderma. • Reflux may cause esophagitis, stricture, ulceration, *or columnar metaplasia of esophageal squamous epithelium (Barrett esophagus).* • ***24 hour pH monitoring—most accurate investigation*** *Endoscopy—investigation of choice*

Achalasia	• Motility disorder with 3 abnormalities:
	  ◦ *Failure of relaxation of LES (↑LES tone) due to loss of ganglion cells in Myenteric (Auerbach) plexus*
	  ◦ *High LES resting pressure*
	  ◦ *Aperistalsis*
	• *Which leads progressive **dysphagia to solids and liquids** (while in obstruction—solids only—then may progress to liquid dysphagia as well).*
	• Investigation:
	  ◦ CXR----------------no air in stomach, dilated esophagus
	  ◦ *Barium studies----------------esophagus terminates in narrowing at LES **("bird's beak appearnce")***
	  ◦ ***Manometry----------------Definitive diagnosis***
	• *Associated with ↑risk of esophageal squamous cell carcinoma.*
	• Secondary achalasia may arise from Chagas disease (T. cruzi infection).

Barrett Esophagus	• Pre-malignant condition in which the squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium containing goblet and columnar cells (specialized intestinal metaplasia) • It presents as a complication of long standing GERD (10% cases) • Diagnosis:-----------------Endoscopic biopsy • Associated with Esophagitis, Esophageal ulcers, *and ↑risk of esophageal adenocarcinoma.* • Management

Management of Barrett Esophagus

Barrett metaplasia without dysplasia	High-dose PPI and endoscopy every 3-5 years recommended to look for low- or high-grade dysplasia or adenocarcinoma.
Low grade dysplasia	High-dose PPI + endoscopic surveillance in 6 months to exclude coexisting high-grade dysplasia or cancer
High grade dysplasia	High-dose PPI + Endoscopic ablation/resection is the treatment of choice

Esophageal Carcinoma

Type	Location	Features
Squamous Cell Carcinoma	*Upper 2/3rd*	• Typically presents with progressive *Dysphagia (**first solids, then liquids**)* and weight loss; poor prognosis. • *Worldwide, squamous cell is more common.*
Adenocarcinoma		• *Adenocarcinoma is most common type in America* • Risk Factors:

Squamous cell CA	Adenocarcinoma
Achalasia, Alcohol, Hot liquids, Cigarettes	*Barrett esophagus, obesity, GERD, Cigarettes*

Comparison of Esophageal Motility Disorders

Disorder	Achalasia	Diffuse Esophageal Spasm & Nut cracker esophagus	Scleroderma
Definition	• Failure of Lower Esophageal sphincter (LES) to relax with swallowing Aperistalsis in the distal two-third Increased resting tone of LES	• It is a motility disorder in which normal peristalsis is periodically interrupted by high amplitude non-peristaltic contractions • **Nutcracker esophagus** ◦ A variant of diffuse esophageal spasm ◦ Rare condition characterized by forceful peristaltic activity leading to episodic chest pain and dysphagia showing very high-amplitude peristalsis (pressures >200 mmHg) on manometry	• Systemic disease characterized by vasculopathy and tissue fibrosis (especially skin thickening)
Diagnosis	• Barium studies: ***Birds beak appearance*** • Manometry = ***Inc. resting pressure in LES*** & Dec. peristalsis in the body of esophagus	• Barium X ray= **Corkscrew appearance** • Manometry= >30% (but <100%) of esophageal contractions are aperistaltic	• Clinical features of scleroderma • Manometry: **decreased pressure in LES,** decreased peristalsis in body of esophagus
Treatment	• Botulinum toxin injection • Pneumatic dilation • Heller cardiomyotomy	• Ca++ channel blockers Nitrates Pneumatic dilation surgical Myotomy	• Medical: aggressive GERD therapy (PPIs bid) • Surgery: anti-reflux surgery (gastroplasty, last resort)

Diseases of Stomach

Ménétrier disease		• Also known as hypertrophic gastropathy, results from hyperplasia of surface mucous cells with glandular atrophy
		• Features:
		  ◦ Gastric secretions contain excess mucous and lack of HCL
		  ◦ Malignant transformation

Acute Gastritis		• Causes:
		  ◦ Nonsteroidal anti-inflammatory drugs (NSAIDs)
		  ◦ Cigarette smoking
		  ◦ Heavy alcohol intake
		  ◦ **Burn** injury: **Curling** ulcer→association with severe burns
		  ◦ **Brain** injury: **Cushing** ulcer→association with brain injury
		• (**Burned** by the **Curling** iron. Always **Cushion** the **brain**).

Chronic Gastritis	Non-atrophic	• *H. pylori*
	Atrophic	(see table below)

Type A chronic gastritis	Type B chronic gastritis
• It is autoimmune atrophic gastritis	• It is H. pylori atrophic gastritis
• **Involves body and fundus**	• **Involves antrum and pylorus**

• Characterized by
  ◦ Autoantibodies to parietal cells
  ◦ *Pernicious Anemia*
  ◦ Achlorhydria.
	• *Most common type*

Associations: DM type-1, Addison disease, Hashimotos thyroiditis	Associations: duodenal, gastric ulcers or **gastric MALToma**

Peptic Ulcer

- Characterized by formation of ulcers that occur in any portion of GIT.
- **Location:**
  - *Duodenum: first portion of duodenum (most common)*
  - *Stomach: lesser curvature within the antrum (most common)*
  - Gastroesophageal junction
  - Within or adjacent to ileal Meckel diverticulum.
- **Causes:**
  - H. pylori infection:
    - Gram negative rod
    - Produces ureases, Increased permeability of the gastric mucosa to hydrogen ion, resulting in back diffusion of hydrogen ion with injury to the gastric mucosa
  - Steroids, Smoking and Increase acid production:
    - *Except for peptic ulcer of the stomach, peptic ulcer is always associated with hypersecretion of gastric acid and pepsin.*
- **Ulcer properties:**

Duodenal ulcers	Gastric ulcers
• Can occur in age group but most common in 30-55 years	• Can occur in age group but most common in 50-75 years
• *Duodenal ulcer pain Decreases with food*	• *Gastric ulcer pain Grows with food*
• Virtually Never malignant	• **Associated with increased risk of malignancy**
• Hemorrhage→*(posterior>anterior).from erosion of gastroduodenal artery*	• Hemorrhage→from erosion of left gastric artery

H. Pylori Tests

Test	Advantage	Disadvantages/Explanation
	Non-invasive	
Serology (H. pylori antibodies test)	Cheapest non-invasive test	• The antibody remains detectable as long as 18 months after successful eradication, and cannot be used to document successful eradication of the organism
Urea breath test	Most accurate non-invasive test for diagnosis	• Proton pump inhibitors may cause false-negative urea breath tests and fecal antigen tests and should be withheld for at least 14 days before testing.
Fecal antigen test	Has high sensitivity and specificity, can confirm eradication of H. pylori.	• **Both urea breath test and fecal antigen test has sensitivity and specifity of 95% can be done to document successful eradication of h. pylori**
	Invasive	
Endoscopic biopsy	Gold standard for diagnosis of peptic ulcers	
Rapid urease test		The test may be falsely negative if patients are taking PPIs or antibiotics at the time.
Microbiological culture		This technique is typically used for patients with refractory H. pylori infection to identify the appropriate antibiotic regimen

Gastric Malignancy

<table>
<tr><th>Type</th><th>Features</th></tr>
<tr><td>Gastric Carcinoma</td><td>

Risk factors:

H. Pylori (most common)
Smoked fish, meat and pickled vegetables
Nitrosamines—from dietary amines and nitrites (food preservative).
Blood group A
HNPCC

Histologically, stomach carcinoma is almost always adenocarcinoma.
Morphological variants:

<table>
<tr><th>Intestinal</th><th>Diffuse</th></tr>
<tr><td>

Associated with H. pylori
The intestinal variant can become ulcerated and must be differentiated from peptic ulcer.
Peptic ulcer usually exhibits a smooth base with nonelevated, punched-out margins. In contrast, carcinoma ulcers has necrotic base and raised margins
</td><td>

Not associated with H. pylori
Signet ring cells (mucin-filled cells with peripheral nuclei),
Stomach wall grossly thickened and leathery (linitis plastic—thickened leather bottle like stomach)
</td></tr>
</table>

Metastasis:

Direct: Pancreases, colon and liver
Lymphatic spread:

Left supraclavicular node (Virchow node)
Periumbilical region (Sister Mary Joseph nodule)
Ovaries (krukenberg tumor-- displacing the nucleus to one side and resulting in so-called signet-ring cells.)

</td></tr>
</table>

Gastric Lymphoma (MALToma)	• *Only malignancy that can be treated with antibiotics* • *Associated with H. Pylori*
Gastrointestinal Stromal Tumors (GIST)	• *Mesenchymal tumors derived from the pace- maker cells of Cajal* *Treatment involves surgical resection and treatment with imatinib*

Malabsorption Syndrome

- Can be caused by
  - Disorders of mucosa→celiac disease, whipple disease, tropical sprue
  - Disorders of intraluminal digestion→lactose intolerance, pancreatic insufficiency
- How to differentiate b/w these two:
  - d-xylose absorption test:
    - Normal urinary excretion in pancreatic insufficiency
    - ↓Excretion with intestinal mucosa defects or bacterial overgrowth.
- Can result in:
  - Can cause diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiencies

Celiac Disease (aka **as sprue, gluten sensitive enteropathy)**	• *Also known as gluten sensitive enteropathy*
	• *Celiac disease is caused by sensitivity to gluten in cereal products*
	• Clinical manifestations include weight loss, weakness, and diarrhea with pale, bulky, frothy, foul-smelling stools.
	• In children, it is also characterized by growth retardation and general failure to thrive.
	• Associated with:
	  ◦ *Type I diabetes mellitus*
	  ◦ HLA-DQ2, HLA-DQ8
	  ◦ *Dermatitis herpetiformis*
	  ◦ ↓Bone density
	• Lab findings:
	  ◦ *Anti-endomysial, anti-tissue transglutaminase, and anti-gliadin antibodies*
	  Duodenal biopsy (gold standard) which shows
	    ▪ *Blunting of villi*
	    ▪ *Lymphocytes in lamina propria*
	    ▪ *Crypt hyperplasia*
	• Moderately↑risk of malignancy (e.g., T-cell lymphoma)

Whipple Disease	*(Mnemonic: **FOAMY WH**ipped cream **PAS**sed in a **CAN**)*
	• *Characterized by infiltration of small intestinal mucosa by **FOAMY** macrophages (Tropheryma **WHIP**plei) that stain positive with **PAS** reagent Infection*
	• **C**ardiac symptoms, **A**rthralgias, and **N**eurologic symptoms are common.
	• Diagnosis
	  ◦ Jejunal biopsy—shows macrophages containing PAS
	  Diagnosis made by Tissue PCR
	• Management:
	  ◦ **IV penicillin** plus **streptomycin 2 weeks** then
	  ◦ oral **co-trimoxazole or tetracyclin** for a year (have the lowest relapse rate)

Disaccharidase Deficiency	• Lactase deficiency→milk intolerance.
	Lactase is brush border enzyme of villous absorptive epithelial cells.
	Features:
	  ◦ Normal-appearing villi.
	  Osmotic diarrhea.
	  Since lactase is located at tips of intestinal villi, self-limited lactase deficiency can occur following injury (e.g., viral enteritis).

	• Diagnosis:
	  • Hydrogen breath test
	  Lactose tolerance test: ⊕ for lactase deficiency if administration of lactose produces symptoms and serum glucose rises < 20 mg/dL

Pancreatic Insufficiency	• *Due to cystic fibrosis,* obstructing cancer, chronic pancreatitis. Results in malabsorption of fat and fat-soluble vitamins (A, D, E, and K) as well as vitamin B12. ↑Neutral fat in stool.

Inflammatory Bowel Disease

- Chronic inflammatory condition of unknown etiology may affect any part of the gastrointestinal tract
- Represented by
    - Crohns disease
    - Ulcerative colitis

	Ulcerative Colitis	UlceratCrohn's diseaseive Colitis
Definition	• A chronic inflammatory disease that is characterized by inflammation and can involve colon only	• A chronic inflammatory disease, that can involve entire gut- from mouth to anus—but rectum generally spared
Epidemiology	• Males and females appear equally affected • Smoking has protective effect	• Female > male Strong association with smoking
Features	• Inflammation limited to mucosa and submucosal • *No skip lesions* • *No granulomas* • Crypt abscess • Psuedopolyps	• Transmural inflammation *Rose thorn ulcers* *Skip lesions due to discontinuous spread* *Non-caseating Granulomas* Regular abscess *Cobble-stone appearance*
Clinical features	• Malaise, fever, weight loss----- Sometimes • Rectal bleeding ----Nearly always	• Malaise, fever, weight loss---- Common Rectal bleeding -----Sometimes *Abdominal mass palpable in RIF*
Extra intestinal manifestation and Complications	***Mnemonic: U-PAST-Colitis*** • *Uveitis* • *Pyoderma gangrenosum* • *Arthritis (most common overall)* • *Ankylosing spondylitis* • *Primary Sclerosing cholangitis* • *Toxic megacolon* • *Colon carcinoma*	*Mnemonic:* ***PIE SAC*** • *vPerianal disease ----Anal fissure, anal **fistulas*** • *vErythema nodosum* • *vStrictures* • *vAphthous ulcers, **Arthritis** (most common overall)* • *Calcium oxalate stones ----renal stones*
Radiography	• Lead pipe appearance	• String sign

Investigation	• Serological testing
	  • *Antineutrophil cytoplasmic antibody*
	  • *(ANCA) –Positive in UC*
	• Colonoscopy with biopsies confirms the diagnosis
		• Serological testing
		  • *Anti-Saccharomyces cerevisiae antibody (ASCA--- Positive in CD*
		• Colonoscopy with biopsies confirms the diagnosis

Treatment	• 5-aminosalicylic preparations (e.g., mesalamine), 6-mercaptopurine, infliximab, colectomy	• Corticosteroids, azathioprine, antibiotics (e.g., ciprofloxacin, metronidazole), infliximab, adalimumab
Mnemonic	**Mnemonic: ULCCCERS** • Ulcers, Large intestine, Continuous, Colorectal carcinoma, Crypt abscesses, xtends proximally, Red diarrhea, Sclerosing cholangitis	**Mnemonic: CHRISTMAS** • Cobble stone, High temperature, Reduced lumen, Intestinal lumen, Skip lesions, Transmural, Malabsorption, Abdominal pain, Submucosal fibrosis

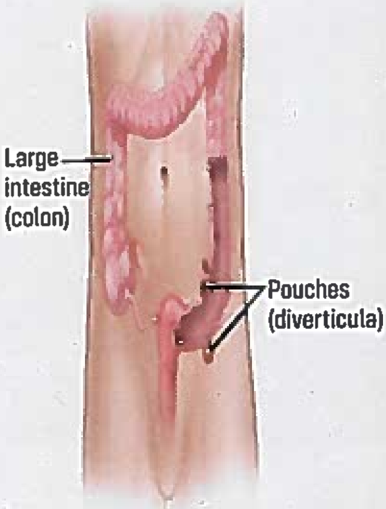
Diseases of Colon

Irritable Bowel Syndrome

- Recurrent abdominal pain associated with ≥ 2 of the following:
    - Pain improves with defecation
    - Change in stool frequency
    - Change in appearance of stool
- No structural abnormalities.

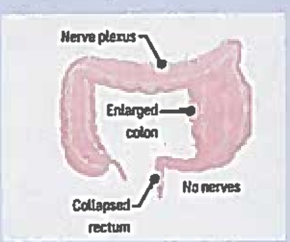
May present with diarrhea, constipation, or alternating symptoms

Diverticula



- **Diverticulum:**
    - Blind pouch protruding from the alimentary tract that communicates with the lumen of the gut.
    - Most diverticula (esophagus, stomach, duodenum, and colon) are acquired and are termed "false" in that they lack or have an attenuated muscularis externa.
        - "True" diverticulum—all 3 gut wall layers outpouch (e.g., Meckel).
        - "False" diverticulum or pseudodiverticulum—only mucosa and submucosa outpouch. Occur especially where vasa recta perforate muscularis externa
    - Most frequently involve the sigmoid colon
- **Diverticulitis:**
    - Inflammation of diverticula classically causing LQ pain, fever, leucocytosis.
    - May perforate→peritonitis, abscess formation, or bowel stenosis.
    - *Sometimes called "left-sided appendicitis" due to overlapping clinical presentation.*

Hirschsprung Disease (Congenital Megacolon)



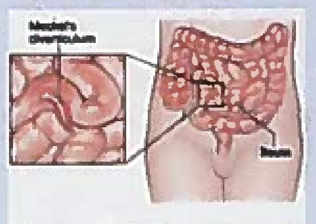
- *Dilation of the colon due to the absence of ganglion cells of the submucosal and Myenteric neural plexuses; dilation is proximal to the aganglionic segment.*
- Due to failure of neural crest cell migration.
- Associated with mutations in the RET gene.
- Presents with bilious emesis, abdominal distention, and failure to pass meconium
- *Risk↑with Down syndrome.*
- Diagnosed by rectal suction biopsy.

Treatment: resection

Pseudomembranous Colitis

- This condition is morphologically distinguished by superficial greyish mucosal exudates consisting of necrotic, loosely adherent mucosal debris (pseudomembrane).
- The cause most often is overgrowth of exotoxin-producing ***Clostridium difficile***.
- Clinical characteristics include fever, toxicity, and diarrhea, most often occurring in patients on broad-spectrum antibiotic therapy

Meckel diverticulum



- Most common congenital anomaly of the small intestine
- *Persistence of the vitelline duct.*

***The rule of 2's:** 2 times as likely in males, **2** inches long, **2** feet from the ileocecal valve, Commonly presents in first **2** years of life, May have **2** types of epithelia (gastric/ pancreatic).*

- Usually asymptomatic

Tumors of Colon

Polyp (A polyp is a descriptive term for any elevation of the intestinal surface)

Benign Polyp	• Non-neoplastic polyps: ◦ Hyperplastic polyps. Inflammatory psuedopoly→psassociated with UC. • Hamartomatous polypsAssociated with Peutz-Jeghers syndrome and juvenile polyposis
Benign Polyp	• True neoplasm- i.e., neoplastic, having following forms • Tubular adenomas (most common type 75%) • Tubulovillous adenomas • Villous adenomas (↑risk of malignancy)

Polyposis Syndrome

Familial Adenomatous Polyposis (FAP)	• Autosomal dominant condition characterized by the presence of hundreds to thousands of adenomatous polyps. • *The germline defect is in the APC gene on chromosome.* • The risk of malignant transformation approaches 100%.
Gardner Syndrome	• Variant of FAP • Characterized by the presence of numerous adenomatous polyps along with osteomas and soft tissue tumors
Turcot Syndrome	• Variant of FAP • Characterized by adenomatous polyps along with tumors of the central nervous system (especially medulloblastoma).
Peutz-Jeghers Syndrome	• Autosomal dominant syndrome • *Numerous hamartomas throughout GI tract, along with **hyperpigmented** mouth, lips, hands, genitalia.* • Associated with↑risk of colorectal, breast, stomach, small bowel, and pancreatic cancers. • Colonoscopy every 2 years after the age of 25 years for evaluation of the presence of polyps and polypectomy.
Juvenile Polyposis Syndrome	• Autosomal dominant syndrome in children (typically < 5 years old) • Numerous hamartomatous polyps in the colon, stomach, small bowel. • Associated with↑risk of CRC
Lynch Syndrome	• Previously known as hereditary nonpolyposis colorectal cancer (HNPCC). • **Autosomal dominant** • 80% progress to CRC. • Proximal colon is always involved. • Associated with endometrial, ovarian, and skin cancers. • Can be identified clinically in families using **3-2-1 rule:** ◦ **3** relatives with Lynch syndrome– associated cancers across **2** generations, **1** of whom must be diagnosed before age 50 years.

Mesenteric Ischemia

Acute Mesenteric Ischemia	• *Critical blockage of intestinal blood flow (often embolic occlusion of SMA) resulting in small bowel necrosis* • Findings: Abdominal pain, red "currant jelly" stools may be seen.
Chronic Mesenteric Ischemia	• *"Intestinal angina": atherosclerosis of celiac artery, SMA, or IMA resulting in intestinal hypoperfusion* • Findings: postprandial epigastric pain

Colorectal cancer (adenocarcinoma of rectum and colon)

Predisposing factors	• Adenomatous polyps, Inherited multiple polyposis syndromes, Long-standing ulcerative colitis, Genetic factors, low-fiber diet
Characteristics	• Right side bleeds; left side obstructs
Diagnosis	• *Apple core" lesion seen on barium enema x-ray* *Unexplained iron deficiency anaemia in men or non-menstruating women (Hb < 11 g/dl in men, < 10 g/dl in women) raises suspicion* *CEA tumor marker:* good for monitoring recurrence, not useful for screening. ***Colonoscopy:*** • *Screen low-risk patients starting at age 50 with Colonoscopy* (alternatives include flexible sigmoidoscopy, fecal occult blood testing (FOBT), CT colonography. • *Patients with a first-degree relative who has colon cancer should be screened via colonoscopy at age 40, or starting 10 years prior to their relative's presentation.*
Staging Colorectal Cancer	

Dukes' A	Carcinoma in situ limited to mucosa or sub mucosa	Surgery only
Dukes' B	Invasion through the bowel wall but not involving lymph nodes	Surgery then radiotherapy
Dukes' C	Involvement of lymph nodes	Surgery plus chemotherapy & Radiotherapy may be needed
Dukes' D	Widespread metastases.	Surgery to remove the tumour or to bypass an obstructing tumour, Palliative chemotherapy and/or radiotherapy for symptom relief;

Refeeding syndrome

- Refeeding syndrome describes the metabolic abnormalities which occur on feeding a person following a period of starvation.
- The metabolic consequences include:
  - Hypophosphatemia, Hypokalaemia, Hypomagnesaemia, Abnormal fluid balance.
- These abnormalities can lead to organ failure.
- Prevention (NICE guidelines)
  - **Patients are considered high-risk, If one or more of the following:**
    - BMI < 16 kg/m2
    - Unintentional weight loss >15% over 3-6 months
    - Little nutritional intake > 10 days
    - Hypokalaemia, hypophosphataemia or hypomagnesaemia prior to feeding
- **NICE recommend that if a patient hasn't eaten for > 5 days, aim to re-feed at no more than 50% of requirements for the first 2 days.**

Diseases of Liver

Jaundice

- Refers to yellow discoloration of skin, sclera and mucous membrane
- *Usually detectable when plasma bilirubin exceeds 3mg/dl*

Unconjugated Hyperbillirubinemia	• 2 types→Hemolytic jaundice and congenital non hemolytic jaundice
	• Hemolytic jaundice:
	  ◦ Due to↑production of UCB from hemolysis.
	  ◦ Caused by: sickle cell anemia, hereditary spherocytosis, hemolytic disease of newborn etc.
	• Congenital non-hemolytic anemia:
	  ◦ Due to↓uptake or conjugation of UCB

Crigler-najjar syndrome-I	Crigler-najjar syndrome-II	Gilbert syndrome
• *Autosomal recessive* • *UDP-glucoronyl transferase absent* • May lead to kernicterus	• *Autosomal dominant* • *UDP-glucoronyl transferase decreased* • Mild jaundice, no kernicterus • Treatment= oral phenobarbital	• *Autosomal dominant* • *UDP-glucoronyl transferase decreased* • *Occurs in adults in response to alcohol, fasting, and strenuous exercise.*

Hepatocellular Jaundice	• Due to inability of liver to transport bilirubin into bile, as a consequence of parenchymal liver disease • *Causes mixed hyperbillirubinemia i.e. elevation of both UCB and CB* • *In viral hepatitis: ALT>AST, mild elevation of ALP and GGT* • *Alcoholic hepatitis: AST>ALT, mild elevation of ALP and GGT*

Conjugated Hyperbillirubinemia (Cholestatic (Obstructive) Jaundice)	**Decreased intra-hepatic bile flow**	**Decreased extra hepatic bile flow**
	• Primary biliary cirrhosis Autoimmune hepatitis Congenital conjugated hyperbillirubinemia 1. Dubin-johnson syndrome: *Defective bilirubin transport, black liver-due to dark pigment granules deposition* 2 Rotor syndrome: *Same as Dubin-johnson syndrome but no black liver.*	• Carcinoma of head of pancreases • Biliary strictures • Choledocholithiasis

Jaundice Lab Findings

- *AST is present in mitochondria while ALT is present in cytosol*

Unconjugated hyperbillirubinemia	• *AST elevated*
Alcoholic hepatitis	Mnemonic: Make a to**AST** with **alcohol** • ***AST** >>ALT, because alcohol is mitochondrial toxin*
Viral hepatitis	• *ALT>>AST, because virus causes liver cell necrosis*
Obstructive	• *Marked elevation of ALP and GGT*
Remember	• *↑ALP + ↑GGT= cholestatic jaundice* *↑ALP + normal GGT= source other than liver e.g. Bones*

Hepatitis

Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E	Alcoholic Hepatitis	Autoimmune Hepatitis
HAV-RNA virus	*HBV-DNA virus*	HCV-RNA virus	HDV-RNA virus	HEV-RNA	Fatty change Focal liver cell necrosis infiltrates of neutrophils *intracytoplasmic inclusions (Mallory bodies)*	*Increased serum immunoglobins and anti-smooth muscle antibodies*
Orofecal route	Parenteral Sexual Vertical (mother to neonate)	Parenteral Sexual Vertical (mother to neonate)	*Highest fatality rate*	Orofecal route		
No chronic state	Carrier stage	Carrier stage	Association with HBV	*Fulminant hepatitis in pregnant women*		
No HCC	*HCC (major association)*	HCC	Incidence↑ in IV drug users			
	Associated with Polyarteritis nodosa Aplastic anemia	***Associated with↑risk B-cell NHL, ITP, autoimmune hemolytic anemia***		virus		

Serological Patterns Of Hep-B

STAGE	HBsAg	HBeAg	Anti-HBc	Anti-HBs
Acute Infection	positive	positive	positive (IgM)	Negative
Chronic Infection	positive	positive	positive (IgG)	Negative
Immune From Previous Infection	Negative	Negative	positive	positive
Immune From Vaccination	Negative	Negative	Negative	positive
Window Period	Negative	Negative	positive (IgM)	Negative

Immunization:

- 3 doses, at 0, 1 and 6 month, and a booster dose after 5 years

Testing for anti-HBs:

- Only recommended for those at risk of occupational exposure (i.e. Healthcare workers) and patients with CKD.
- In these patients anti-HBs levels should be checked 1-4 months after primary immunization

Anti-HBs level (mIU/ml) Response

> 100	Indicates adequate response	No further testing required. Should still receive booster at 5 years
10-100	Suboptimal response	One additional vaccine dose should be given If immunocompetent no further testing is required
< 10	Suboptimal response	Test for current or past infection. • Give further vaccine course (i.e. 3 doses again) with testing following. • If still fails to respond then HBIG would be required for protection if exposed to the virus

Non-Alcoholic Fatty Liver Disease and Alcoholic Fatty Liver Disease

Non-Alcoholic Fatty Liver Disease	Alcoholic Liver Disease
• Risk factors: ◦ Metabolic syndrome (insulin resistance) ◦ Obesity→fatty infiltration of hepatocytes • *Most common cause of Cryptogenic Cirrhosis.* Increased risk of HCC	• Occurs in 3 forms ◦ Alcoholic steatosis (alcoholic fatty liver disease) ◦ Alcoholic hepatitis ◦ Alcoholic cirrhosis **Alcoholic Steatosis**: • Macrovesicular fatty change. • That may be reversible with alcohol cessation. **Alcoholic Hepatitis**: • Long-term consumption. • Swollen and necrotic hepatocytes with neutrophilic infiltration. • ***Mallory bodies*** (intracytoplasmic eosinophilic inclusions of damaged keratin filaments). **Alcoholic Cirrhosis**: • Final and usually irreversible form. • Regenerative onodules→ chronic liver injury→↑portal hypertension and end-stage liver disease. • **Sclerosis around central vein**
• *(ALT > AST (Lipids)*	• ***AST** >>ALT (Make a to**AST** with **alcohol**)*
	• ***NOTE:** It causes macrocytic anemia, not megaloblastic anemia, therefore no hypersegmented neutrophils*

Hepatic Encephalopathy

- Cirrhosis→portosystemic shunts→↓NH3 metabolism→neuropsychiatric dysfunction.
- Reversible neuropsychiatric dysfunction ranging from disorientation to difficult arousal or coma.
- **Triggers:**
  - ↑NH3 production and absorption (due to dietary protein, GI bleed, **constipation**, infection).
  - ↓NH3 removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS).\
- **Grades of hepatic encephalopathy**

Grade 0	Minimal alterations and impairment of executive function
Grade 1	Drowsy, sleep abnormalities (sleep inversion), irritability, poor concentration
Grade 2	Lethargy, apathy and drowsiness
Grade 3	Stupor, Depressed conscious levels but arousable
Grade 4	Coma with no response to painful stimuli

- **Treatment:**
  - Correction of hypoglycaemia--- 10% dextrose can be used
  - Treat any precipitating cause if any
  - *Lactulose (↑NH_4^+ generation) and rifaximin or neomycin (↓NH_3 producing gut bacteria).*

Bacterial Peritonitis

Primary/Spontaneous Bacterial Peritonitis (SBP)	• Complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed • **Clinical features:** fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury • **Causative agent:** Gram-negatives compose 70% of pathogens: *E. coli (most common), Streptococcus, Klebsiella* • **Diagnosis:** Paracentesis with ascitic fluid absolute neutrophil count (ANC) > 250 cells/mm3.
Secondary Bacterial Peritonitis	• Usually results from a perforated viscus or surgical manipulation *Most common aerobe: E. coli, while most common anerobe: Bacteroides*

Cirrhosis

- It is end stage liver disease characterized by irreversible diffuse fibrosis with formation of regenerative nodules
- ↑ Risk for hepatocellular carcinoma (HCC).
- Decompensated cirrhosis refers to cirrhosis in association with jaundice, variceal hemorrhage, ascites or encephalopathy

Causes	• *Viral hepatitis (B and C)→most common cause worldwide* • *Alcoholic liver disease (most common)→most common in west* • Primary biliary cirrhosis and sclerosing cholangitis • Autoimmune hepatitis • *Wilson disease* • α1-antitrypsin deficiency • *Cryptogenic cirrhosis (non-alcoholic fatty liver disease)*
Clinical Manifestation	• Jaundice • Hypoalbuminemia, caused by decreased albumin synthesis in damaged hepatocytes • Coagulation factor deficiencies→*caused by decreased synthesis, all coagulation factors (with the exception of von Willebrand factor) are synthesized in the liver)* • Hyperes→trinismmanifests as *palmar erythema* (liver palms); spider nevi (capillary telangiectasia) of the face, upper arms, and chest; loss of body and pubic hair; testicular atrophy; and gynecomastia. • Neurological symptoms→*hepatic encephalopathy* (from slight confusion to deep coma, due to ↑NH_3 production and less removal), Asterixis ("flapping tremor") • *Effects of portal hypertension→Esophageal varices→ hematemesis*

Vascular Disorders of Liver

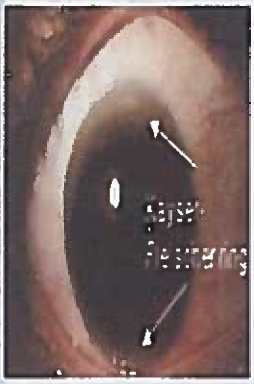
Portal hypertension	• Characterized by the development of venous collaterals with varices in the submucosal veins of the esophagus, the hemorrhoidal plexus, and other sites.
	• This condition is often classified by the site of portal venous obstruction:
	• Causes:
	  ◦ Prehepatic:o caused by portal and splenic vein obstruction, most often by thrombosis Intrahepatic: caused by intrahepatic vascular obstruction, most often by cirrhosis or
	  ◦ Metastatic tumor, and more rarely by exotic entities such as schistosomiasis
	  ◦ Posthepatic: caused by venous congestion in the distal hepatic venous circulation,
	• Most often as a result of constrictive pericarditis, tricuspid insufficiency, congestive heart failure, or hepatic vein occlusion (budd-chiari syndrome)

Infarction	• Is unusual, because the liver has a double blood supply (mesenteric and hepatic).

Budd-Chiari syndrome	• *The cause is thrombotic occlusion of the major hepatic veins, resulting in abdominal pain, jaundice, hepatomegaly, ascites, and eventual liver failure.* • Budd-Chiari syndrome is most often associated with polycythemia Vera, hepatocellular carcinoma, and other abdominal neoplasms; may also occur as a complication of pregnancy.
Congestive Heart Failure	• In long-standing chronic right-sided heart failure, the cut surface of the liver can assume an appearance referred to as "nutmeg liver," with dark red congested centrilobular areas alternating with pale portal areas. • Eventually, centrilobular fibrosis occurs, resulting in cardiac cirrhosis (cardiac sclerosis). • Similar changes may follow long-standing constrictive pericarditis or tricuspid insufficiency.

Miscellaneous Topics

Wilson disease



- Also known as hepatolenticular degeneration.
- *Autosomal recessive disorder of copper metabolism resulting in accumulation of toxic levels of copper.*
- Normally: copper is absorbed in small intestine, taken into liver, where it is stored and incorporated into ceruloplasmin.
- In Wilson's disease: *copper incorporation into ceruloplasmin and its excretion into bile are impaired resulting in copper accumulation in liver*
- Clinical manifestations:
  - Liverhepatitis, fulminant hepatic failure, *Micronodular cirrhosis.*
  - Eyes *Kayser-Fischer rings* (greenish-brown discoloration of cornea)
  - CNS tremors, parkinsonism
- Diagnosis:
  - ***Decreased serum ceruloplasmin, ↑urinary excretion of copper, liver biopsy***

Hemochromatosis

Definition

- Excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total body stores

Etiology:

- Primary (Hereditary) Hemochromatosis
  - *Most often caused by a mutation in the Hfe-gene on chromosome 6.*
- Secondary hemochromatosis
  - *Parenteral iron overload (e.g. transfusions), Chronic hemolytic anemia: thalassemia, Excessive iron intake*

Clinical features: Mnemonic ABCCDH

- Joints: ---Arthralgia (any joint, but especially MCP joints)
- Skin: ---- Bronze or grey (due to melanin, not iron)
- heart: ----Cardiomyopathy (dilated)
- Liver: ----Cirrhosis (30%), HCC (200x increased risk)
- Diabetes
- Hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea).

Can be identified on biopsy with Prussian blue stain.

Biliary tract disease

- Clinical features:
  - Pruritus, jaundice, light-colored stool, dark urine, hepatosplenomegaly.
  - Typically, with cholestatic pattern of LFTs (↑conjugated bilirubin, ↑cholesterol, ↑ALP).

Primary Sclerosing Cholangitis	• Is rare except in association with inflammatory bowel disease, especially ulcerative colitis. • Characteristics include inflammation, fibrosis (classically known as "onion skin fibrosis"), and stenosis of intrahepatic and extrahepatic bile ducts. It eventually develops into biliary cirrhosis. • There is an associated increased incidence of cholangiocarcinoma

Primary Biliary Cirrhosis	• Autoimmune reaction
	• Features: Mnemonic: **3M's**.
	  ◦ *Most common in **M**iddle-aged women.*
	  ◦ *Anti-**M**itochondrial antibodies (98% of patients and are highly specific*
	  ◦ *↑serum Ig**M***
	• Characteristics include *severe obstructive jaundice, itching, and hypercholesterolemia;*
	• Hypercholesterolemia leads to **cutaneous xanthoma formation.**
	• *Associated with other autoimmune conditions (eg, Sjögren syndrome, Hashimoto thyroiditis, CREST, rheumatoid arthritis, celiac disease).*

Secondary Biliary Cirrhosis	• Due to extrahepatic biliary obstruction,→ductal injury & inflammation. • Complications→*ascending cholangitis and bacterial inflammation of ducts.*

Hepatic Tumors

	Benign tumors
Hemangioma	• Most common benign tumor of the liver.
Adenoma	• The incidence is apparently related to use of oral contraceptives
	Malignant tumors
Hepatocellular carcinoma or hepatoma	• Most common malignant tumor of liver in adults • *Associated with HBV (+/- cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and non-alcoholic fatty liver disease, autoimmune disease, hemochromatosis, α1-antitrypsin deficiency, Wilson disease) and specific carcinogens (e.g., aflatoxin from Aspergillus).* • Findings: jaundice, tender hepatomegaly, ascites, polycythemia, anorexia. • Spreads hematogenously. Diagnosis: ↑***α-fetoprotein***; ultrasound or contrast CT/MRI, biopsy
Cholangiocarcinoma (bile duct carcinoma)	• *It is associated with Clonorchis Sinensis (liver fluke) infestation.* • *Unlike hepatocellular carcinoma, Cholangiocarcinoma is not associated with HBV infection or cirrhosis.*

Diseases of Gall Bladder and Bile Duct

Cholecystitis	• Acute or chronic inflammation of gall bladder • Usually from cholelithiasis, most commonly blocking the cystic duct • Murphy sign ⊕—inspiratory arrest on RUQ palpation due to pain. • ↑ALP if bile duct becomes involved (e.g., ascending cholangitis).

Cholelithiasis (Gallstones)	• Risk factors (**4 F's**): **F**emale, **F**at, **F**ertile (pregnant), **F**orty
	Stone types
	  ◦ Cholesterol stones→often solitary and too large to enter the cystic duct or the common bile duct
	  ◦ Pigment stones→Association often includes hemolytic anemia and bacterial infection
	  ◦ Mixed stones→account for most stones (75% to 80%).Most of these stones are a mixture of cholesterol and calcium salts. Mixed stones can often be visualized radiographically because of their calcium content

	• *Fatty food intolerance is characteristic* • ***Charcot triad of cholangitis: Jaundice, Fever, RUQ pain*** • Complications: Biliary colic, pancreatitis, cholecystitis, malignancy
Porcelain Gallbladder	• Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging • Treatment: prophylactic cholecystectomy due to high rates of gallbladder carcinoma.
Choledocholithiasis	• Presence of gallstone(s) in common bile duct • Results in obstructive jaundice with conjugated hyperbilirubinemia, hypercholesterolemia, increased alkaline phosphatase, and hyperbilirubinuria

Disease of Pancreas

Acute Pancreatitis	• Due to activation of pancreatic enzymes, resulting in autodigestion of the organ, with hemorrhagic fat necrosis and *deposition of calcium soaps*, and sometimes formation of pseudocysts (lined by granulation tissue, not epithelium). • Causes/predisposing factors (**GET SMASHED**) ◦ **G**allstones. ◦ **E**thanol. ◦ **T**rauma. ◦ **S**teroids ◦ **M**umps ◦ **A**utoimmune (PAN) ◦ **S**corpion stings ◦ **H**yperlipidemia./Hypercalcemia ◦ **E**RCP ◦ **D**rugs (including azathioprine and diuretics). • Clinical manifestations include epigastric abdominal pain radiating to back, anorexia, and nausea. • There is an association with increased serum amylase and lipase. • *Characteristics include hypocalcemia caused by loss of circulating calcium into precipitated calcium-fatty acid soaps.*
Chronic Pancreatitis	• Chronic inflammation, atrophy, calcification of the pancreas • Major causes are alcohol abuse and idiopathic. • *Mutations in CFTR (cystic fibrosis) can cause chronic pancreatic insufficiency.* Manifestation → steatorrhea, fat-soluble vitamin deficiency (night blindness, Osteomalacia), diabetes mellitus. • *Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).*
Pancreatic Adenocarcinoma	• Average survival ' 1 year after diagnosis, Very aggressive tumor • Tumors more common in pancreatic head→obstructive jaundice • ***Associated with CA 19-9 tumor marker (also CEA, less specific).*** • Risk factors→Tobacco use, Chronic pancreatitis (especially > 20 years), Diabetes • Presentation: ◦ Abdominal pain radiating to back, Weight loss ◦ Migratory thrombophlebitis—redness and tenderness on palpation of extremities (Trousseau syndrome) ◦ Tumors that obstruct the common bile duct result in an enlarged, distended gallbladder; ◦ obstructing stones do not (Courvoisier law). • Treatment: ***Whipple procedure,*** chemotherapy, radiation therapy

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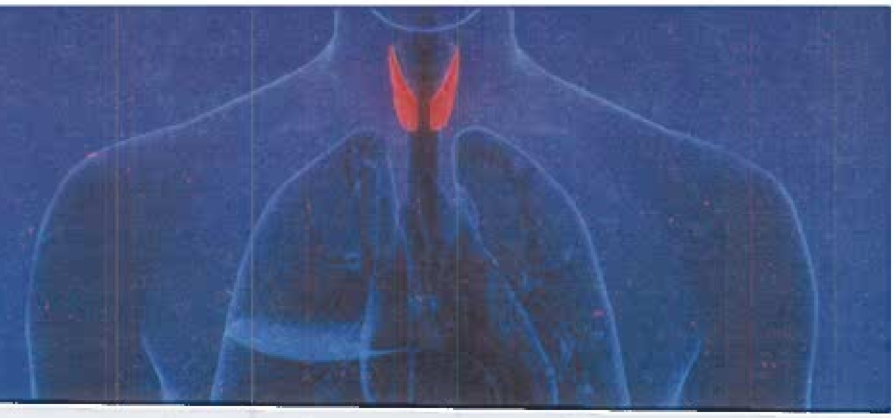


Chapter 7: Endocrinology

Pituitary Gland

Anterior Pituitary (Adenohypophysis)

Hyperpituitarism (hyper secretion of pituitary hormones)

Prolactinoma with hyperprolactinemia

- *Most common pituitary tumor (30% of pituitary tumors).*
- Prolactinoma in women classically presents as galactorrhea, amenorrhea, and ↓ bone density due to suppression of estrogen.
- Prolactinoma in men classically presents as low libido and infertility.
- *Treatment: dopamine agonists (e.g., bromocriptine,), transsphenoidal resection*

Somatotropic adenoma with hypersecretion of growth hormone

- This is the second most common pituitary tumor.
- Gigantism
  - *Results if adenoma develops before epiphyseal closure.*
- Acromegaly
  - *Results if adenoma develops after epiphyseal closure,* Characterized by overgrowth of the jaws, face, hands, and feet, and generalized enlargement of viscera, along with hyperglycemia, osteoporosis, and hypertension.
  - Other results include local compression effects due to expansion of the tumor within the sella turcica.
  - *Treatment: Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog) or pegvisomant (growth hormone receptor antagonist), dopamine agonists (e.g., cabergoline)*

Corticotropic adenoma and hypersecretion of adrenocorticotropic hormone (ACTH)

- Cushing disease
  - *↑ Production of adrenal cortical hormones due to a Corticotropic adenoma of the pituitary.*
- Cushing syndrome
  - *↑ Production of adrenal cortical hormones regardless of cause.*
  - *The cause may be ectopic ACTH production by various tumors (especially small cell carcinoma of the lung).*

Hypopituitarism (Under secretion of pituitary hormones)

- Nonsecreting pituitary adenoma, craniopharyngioma
  Pituitary apoplexy:
  - Sudden enlargement of pituitary tumour secondary to hemorrhage or infarction
  - Characterzed by headachae, vomiting, neck stiffness
- Postpartum pituitary necrosis (Sheehan syndrome)
  - *It is caused by ischemic necrosis of the pituitary gland and is characteristically associated with hemorrhage and shock during childbirth.*
  - Clinical manifestations are due at first to loss of gonadotropins, then to subsequent loss of thyroid-stimulating hormone (TSH) and ACTH.

	• **Empty sella syndrome**
	  ◦ Atrophy or compression of pituitary (which lies in the sella turcica),often idiopathic, common in obese women
	• **Nelson syndrome**
	  ◦ Involves the development of large pituitary adenomas following bilateral adrenalectomy Presents with hyperpigmentation, headaches and bitemporal hemianopia.

Posterior Pituitary (Neurohypophysis)

Syndrome Of Inappropriate ADH (SIADH) Secretion	• SIADH is most commonly caused by ectopic production of ADH by various tumors, *especially small cell carcinoma of the lung.*
	• Clinical features:
	  ◦ Excessive free water retention→Hyponatremia.
	  ◦ Urine osmolality > serum osmolality
	  ◦ Inability to dilute the urine.
	  ◦ Cerebral edema
	  ◦ Neurologic dysfunction
	• Mechanism:
	  ◦ ↑ADH, Excessive free water retention, Body responds to water retention with↓aldosterone→↑urinary Na+ secretion to normalize extracellular fluid volume Very low serum Na+ levels can lead to cerebral edema, seizures
	• Treatment:
	  ◦ **Correction of hyponatremia must be done slowly to prevent osmotic demyelination syndrome (formerly known as central pontine myelinolysis).**
	  ◦ Fluid restriction
	  ◦ **Demeclocycline** (reduces the responsiveness of the collecting tubule cells to ADH

Diabetes Insipidus	• *Lack of ADH (central) or failure of response to circulating ADH (nephrogenic).*
	• Clinical features:
	  ◦ *Polyuria*
	  ◦ *Intense thirst*
	  ◦ *Inability to concentrate urine (dilute urine)*
	• Classification

Types	Central DI	Nephrogenic DI
Findings	• Lack of ADH	• Unresponsiveness of collecting tubules to ADH
Causes	• Pituitary tumor • Head trauma, • Inflammation or tumors of hypothalamus • **DIDMOAD** (or Wolfram's syndrome) is the association of cranial **D**iabetes **I**nsipidus, **D**iabetes **M**ellitus, **O**ptic **A**trophy and **D**eafness	• Genetic • Electrolytes:↑Ca++,↓K+ • Drugs: lithium, demeclocycline (ADH antagonist), ofloxacin
Treatment	• *Desmopressin acetate* • Hydration	• Any underlying cause such as high blood calcium must be corrected to treat NDI. • The first line of treatment is hydrochlorothiazide and amiloride. Consider a low-salt and low-protein diet

Syndrome Of Inappropriate ADH (SIADH) Secretion	• Water deprivation test: · Stage-1: (water deprivation for 0-8 hours): · If after 8 hours, urine concentrates primary polydipsia · If after 8 hours, urine does not concentrates DI (either CDI, NDI) • Stage-2 (give desmopressin 2 ug IM) · If after 8 hours, urine concentrates primary polydipsia · If after 8 hours, urine does not concentrates DI (either CDI, NDI) • Mnemonic: Diabetes Insipidus→Deficient ADH (Central DI) or ADH Doesn't work (Nephrogenic DI), Dilute urine

Thyroid Gland

Hyperthyroidism vs. Hypothyroidism

Mnemonic for Symptoms of hyperthyroidism (SWEATING)

- Sweating
- Weight loss
- Emotional (anxiety)
- Appetite increased
- Tremor/ Tachycardia
- Intolerance of heat/ Irregular menstruation/ Irritability,
- Nervousness
- Goiter and GI problems (diarrhea)

Mnemonic for Symptoms of hypothyroidism (MOM'S Continuously BORED)

- More common in females, occurs mainly in middle life
- Obesity
- Menorrhagia
- Skin and hair dryness
- Constipation
- Bradycardia
- cOld intolerance.
- Raised BP (diastolic)
- Energy levels fall
- Depression/ Delayed relaxation of reflexes

	Hyperthyroidism	Hypothyroidism
General	*Weight loss despite ↑ appetite* *Heat intolerance*	*Weight gain despite ↓ appetite* *Cold intolerance*
Skin	*Sweaty* *Pretibial myxedema*	*Dry skin, dry hairs*
Heart	Systolic hypertension Tachycardia	Diastolic hypertension Bradycardia
Neurological	Anxiety Hyper-reflexia Irritability Tremors	Carpal tunnel syndrome Delayed relaxation of reflexes
Reproductive	*Oligomenorhea, infertility*	*Menorrhagia, infertility*
GIT	Diarrhea	Constipation
Eye	Exophthalmos (graves' disease)	

Labs	↑T3 and T4 ↓TSH	↓T3 and T4 ↑TSH
Causes	• Graves' disease (toxic diffuse goitre) accounts for 50-60% of cases of Thyrotoxicosis. • Toxic nodular goitre • Toxic adenoma • Subacute (De Quervain's) thyroiditis • Post-partum thyroiditis • Amiodarone therapy	• **Primary atrophic hypothyroidism:** • Most common cause • Autoimmune disease. • **Hashimoto's thyroiditis:** • Autoimmune disease as above with goitre (positive microsomal antibodies) • 10 times more common in women • **After thyroidectomy or radioiodine treatment** • **Drug therapy** (e.g. lithium, amiodarone or anti-thyroid drugs such as carbimazole) • **Dietary iodine deficiency**
Treatment	Carbimazole (SE: Agranulocytosis) Propylthiouracil, radioiodine and surgery	Levothyroxine (Side effect atrial fibrillation)

Thyroid gland (continued)

Hyperthyroidism	**Graves' disease** • *Most common cause of hyperthyroidism* • Associated with HLA-DR3 and HLA-B8. • *Type II hypersensitivity reaction* • Thyroid-stimulating immunoglobulin (TSI), an IgG antibody, that binds to TSH receptors and mimics the action of TSH causing ↑ release of thyroid hormone • A similar reaction with thyroid growth immunoglobulin (TGI) stimulates glandular hyperplasia and enlargement. • Besides all other clinical signs and symptoms of hyperthyroidism there is Pretibial myxedema (infiltrative dermopathy) and Exophthalmos
	Thyroid storm • Life-threatening condition, associated with untreated or undertreated hyperthyroidism and significantly worsens in the setting of acute stress such as infection, trauma, and surgery • Presents with tachycardia (>140 bpm), agitation, restlessness, fever, diarrhea, coma, and tachyarrhythmia (cause of death). • Treatments (4 P's) ◦ β-blockers (e.g., Propranolol), Propylthiouracil, Prednisolone, Potassium iodide (Lugol iodine)

	Subacute (De Quervain's) thyroiditis
	• Thought to occur **following viral infection** and typically presents with **hyperthyroidism, Painful goitre, Self-limiting**
	• Treatment:
	  ◦ **Steroids and propranolol**
	  ◦ Carbimazole and PTU are ineffective (As inc hormones are due to destruction not due to inc production)

Hypothyroidism

- *Hypothyroidism manifests as* ***myxedema in adults or as Cretinism in Children***

Myxedema

- Causes
    - Therapy for hyperthyroidism with surgery, irradiation, or drugs, which is a common cause of myxedema in the United States
    - Iodine deficiency
    - Hashimoto thyroiditis
        - ***hypothyroidism + goiter + anti-TPO antibodies***
        - Most common cause of hypothyroidism in iodine-sufficient regions.
        - Autoimmune disorder with antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies.
        - *Associated with ↑ risk of non-Hodgkin lymphoma (typically of B-cell origin).*
        - Histologic findings: Hürthle cells, lymphoid aggregates with germinal centers

Cretinism (Congenital hypothyroidism)

- Causes
    - Iodine deficiency
    - Maldevelopment of the thyroid gland
    - Failure of the fetal thyroid to descend from its origin at the base of the tongue
- Characteristics (6 P's)
    - Poor brain development (Severe mental retardation)
    - Protuberant tongue (Large tongue)
    - Protuberant abdomen, Protruding umbilicus (umbilical hernia)
    - Puffy-faced child

Other Causes Of Hypothyroidism

- Goitrogens (e.g., Amiodarone, lithium),
- *Wolff-Chaikoff effect (thyroid gland down-regulation in response to ↑ iodide).*

Thyroid Cancer

Papillary carcinoma	• General:
	  · Popular (Most common thyroid cancer)
	  · Palpable lymph nodes (Lymphatic metastasis is common)
	  · Post radiation in head and neck (One of the causes)
	  · Peerless prognosis (Excellent prognosis because it's slow growing)
	• Histology:
	  · Popping eyes (Clear nuclei, Orphan Annie Eyes)
	  · Psammoma bodies

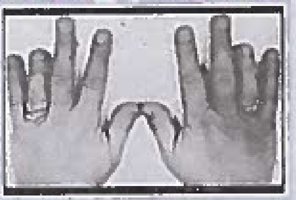
Follicular carcinoma	• *Faraway metastasis (Blood borne metastasis, Invades capsule)* • Uniform Follicles. • Diagnosis relies on the identification of capsular and/or lymphovascular invasion, because these tumors are in all other respects indistinguishable from follicular adenomas
Medullary carcinoma (C-2 , MEN-2)	• Originates from C cells of the thyroid. • *It produces Calcitonin, a Calcium-lowering hormone* • Associated with MEN 2A and 2B

Anaplastic carcinoma	• Tends to occur in older patients and has a very poor prognosis

Parathyroid Glands

Hypoparathyroidism

Hypoparathyroidism	• It refers to ↓PTH secretion → resulting in hypocalcemia
	• Causes:
	  ◦ Accidental surgical excision during thyroidectomy (most common)
	  ◦ *DiGeorge Syndrome (congenital Thymic hypoplasia)*
	• Manifestation:
	  ◦ *Tetany* (intermittent muscular spasms)
	    ▪ *Chvostek sign → tapping of facial nerve causes contraction of facial muscles*
	    ▪ *Trousseau sign → occlusion of brachial artery with BP cuff causes carpal spasm.*

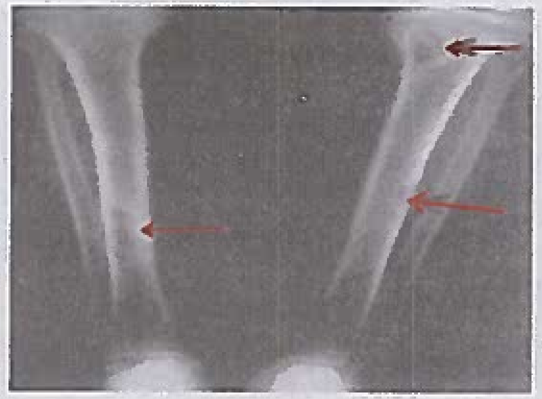
Pseudo Hypoparathyroidism 	• Also known as Albright hereditary osteodystrophy
	• Autosomal dominant condition in which PTH production is normal, but the kidneys are unresponsive to PTH (end-organ resistance to PTH)
	• Manifestation
	  ◦ Short stature
	  ◦ *Short 4th and 5th metacarpals and metatarsals*
	  ◦ *Calcification of basal ganglia*

Hyperparathyroidism

Condition	Causes	S.Ca	S.PO4	PTH	Features
Primary hyperparathyroidism	• Parathyroid adenoma (most common) • Parathyroid carcinoma	↑	↓	↑	Mnemonic: Painful Bones, Renal Stones, Abdominal Groans And Psychic Moans **Painful bones:** fractures, osteoporosis, Osteitis fibrosa cystica **Renal stones** due to ↑Ca++ **Abdominal groans** → constipation due to ↑Ca++ **Psychic moans** → depression, seizures
Secondary hyperparathyroidism	• Chronic renal failure • Vitamin D deficiency	↓	↑	↑	Renal osteodystrophy
Tertiary hyperparathyroidism	• Refractory (autonomous) hyperparathyroidism resulting from chronic renal failure. • Prolonged secondary hyperparathyroidism, in which continuous stimulation results in parathyroid adenoma and autonomous PTH secretion	↑	↑	↑	

Osteitis fibrosa cystica

- A disorder resulting in a loss of bone mass, a weakening of the bones as their calcified supporting structures are replaced with fibrous tissue, and the formation of cyst-like brown tumors in and around the bone, causes bone pain
  It is due to ↑PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism



Renal osteodystrophy

- Is a bone disease that occurs when your kidneys fail to maintain proper levels of calcium and phosphorus in the blood

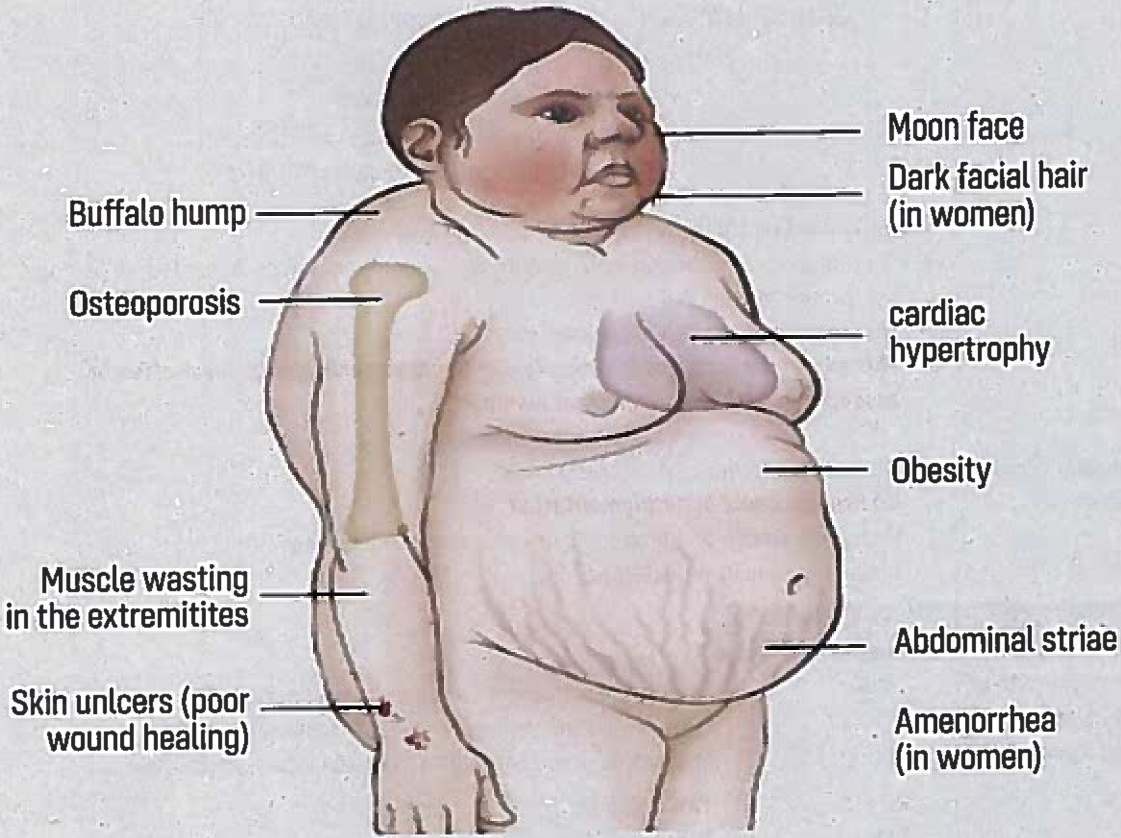
Adrenal Cortex

Cushing Syndrome

Causes	• Exogenous:
	  ◦ *Exogenous corticosteroid medication (most common)*
	• Endogenous causes:
	  ◦ *Cushing disease: ACTH-secreting pituitary adenoma (Most common endogenous cause)*
	  ◦ Adrenal cortical adenoma or adrenal carcinoma
	  ◦ Ectopic production of ACTH small cell carcinoma of the lung

Features	• Non-specific→secondary diabetes, HTN, osteoporosis More specific →*central obesity with extremity wasting, moon facies, buffalo hump* Most specific→spontaneous bruising, *skin striae*, proximal myopathy
Lab values changes	***Mnemonic: Some People Get Cold*** • *Sodium↑* *Potassium↓* *Glucose↑* *Calcium↓*

Diagnosis	• Step-1: To know whether patient has Cushing syndrome
	  ◦ 24 hours urinary free cortisol (best intial test)
	  Dexamethasone suppression test (Most sensitive)
	    ▪ Normal person→suppress cortisol levels
	    ▪ Cushing syndrome→failure to suppress cortisol levels
	• Step:2 To know cause of Cushing syndrome
	  ◦ Measure Plasma ACTH level:
	    ▪ ↓ ACTH level→source is adrenal glands
	    ▪ ↑ACTH level→source is either Pituitary ACTH tumor or Ectopic ACTH production
	• Step: 3 To differentiate between Pituitary and ectopic ACTH production
	    ▪ o48-hour high dose dexamethasone suppression test:
	    ▪ It involves administration of dexamethasone 6 hourly for 48 hours, measuring 24-hour urinary cortisol 2nd day
	    ▪ If ACTH is suppressed→source is pituitary gland, next step is do MRI brain
	    ▪ If ACTH is not suppressed→source is ectopic ACTH, next step is do CT chest/abdomen



Adrenal Cortex (continued)

Hyperaldosteronism

Primary Hyperaldosteronism (Conn syndrome)	• Cause is primary hyper production of adrenal mineralocorticoids • Clinical characteristics include hypertension, sodium and water retention, and hypokalemia • Decreased serum renin occurs due to negative feedback of increased blood pressure on renin secretion • *Findings: ↑aldosterone, ↓renin.*
Secondary Hyperaldosteronism	• This condition is secondary to renal ischemia, renal tumors, and edema (e.g., cirrhosis, Nephrotic syndrome, cardiac failure). • The cause is stimulation of the renin-angiotensin system. • Renin synthesized in the juxtaglomerular apparatus of the kidney promotes the conversion of angiotensinogen to angiotensin I, which is converted catalytically by angiotensin-converting enzyme (mainly in the lung) to angiotensin II. • The release of aldosterone is facilitated by angiotensin II • Findings: ↑aldosterone ↑renin.

Adrenal Insufficiency

Primary Adrenal Insufficiency	**Addison's Disease**
	• Causes:
	  · Idiopathic (most common in developed countries)
	  · Infections e.g. tuberculosis (most common cause overall)
	  · Metastatic tumor
	  · Various infections (e.g. HIV)
	• Characteristics
	  · Hypotension (Postural hypotension)
	  · *Increased pigmentation of skin;*
	  · Serum Na, Cl-, glucose, and HCO_3 decreased
	  · **Serum potassium increased**

	• Diagnosis: · *Short synacthen test (short ACTH- suppression test):* · 250 µg ACTH IM injection given Normal individual→↑cortisol Primary adrenal insufficiency→↑Cortisol Secondary adrenal insufficiency↓ Cortisol
	Waterhouse-Friderichsen Syndrome • This catastrophic adrenal insufficiency and vascular collapse is due to hemorrhagic necrosis of the adrenal cortex. • *This syndrome is often associated with DIC.* • ***This syndrome is characteristically due to meningococcemia, most often in association with meningococcal meningitis.***
Secondary Adrenal Insufficiency	• Seen with↓pituitary ACTH production. ***No skin/mucosal hyperpigmentation*** **No hyperkalemia** (aldosterone synthesis preserved due to intact renin angiotensin-aldosterone axis)

Tumors of the Adrenal Medulla

Pheochromocytoma (Also called paraganglioma)	Causes	• *Most common tumor of the adrenal medulla in adults* • Derived from chromaffin cells (arise from neural crest). • May be associated with MEN 2A, 2B, von Hippel-Lindau disease
	Rule Of 10's	• **10%** malignant • **10%** bilateral • **10%** extra-adrenal (e.g., bladder wall) • **10%** calcify • **10%** kids
	Symptoms	• Episodic hyper adrenergic symptoms (**5P**'s): · **10%** malignant · **10%** bilateral · **10%** extra-adrenal (e.g., bladder wall) · **10%** calcify · **10%** kids
	Lab	• Increased urinary excretion of catecholamines and their metabolites (metanephrine, normetanephrine, and vanillylmandelic acid) is characteristic.
	Treatment	**<u>Mnemonic</u>: Phenoxybenzamine** (16 letters) is given for **Pheochromocytoma** (also 16 letters). • Irreversible α-antagonists (e.g., phenoxybenzamine) followed by β-blockers prior to tumor resection. • **α- blockade must be achieved before giving β-blockers to avoid a hypertensive crisis.**
Neuroblastoma		• *Most common tumor of the adrenal medulla in children, usually < 4 years old*
		• *Abdominal distension and a firm, irregular mass that can cross the midline (while in W ilms tumor, which is renal cancer in children, it is smooth)* • Less likely to develop hypertension than with pheochromocytoma. • **Can also present with opsoclonus-myoclonus syndrome ("dancing eyes-dancing feet").**
		• It is comprised of small round blue cells which form characteristic rosette-like structures ("Homer Wright" pseudorosettes) • Urinary catecholamines and catecholamine metabolites in urine are the same as in pheochromocytoma • ***The tumor is characterized by amplification of the N-myc oncogene***

Adrenal Virilism (Adrenogenital Syndrome)

- Congenital enzyme defects→↓cortisol production and compensatory↑ACTH, with resultant adrenal hyperplasia with androgenic steroid production

Causes	• *21-hydroxylase deficiency (most common)* salt loss and hypotension. 11-hydroxylase deficiencyresults in salt retention and hypertension
Characteristics	• *Virilism in females and precocious puberty in males*

Pancreas

Diabetes mellitus

- Clinical features: *Polyuria, polydipsia, weight loss, blurred vision*

Diagnosis

Criteria-1	• Symptomatic patients plus Abnormal venous glucose on **ONE** occasion i.e. ◦ FBS > 126mg/dL (> 7mmol/L) OR ◦ RBS > 200mg/dL (≥11mmol/L)
Criteria 2	• Asymptomatic patients plus Abnormal venous glucose on **TWO** occasions i.e. ◦ FBS ≥ 126mg/dL (> 7mmol/L) OR ◦ RBS ≥ 200mg/dL (> 11mmol/L)
Criteria 3	• HbA1C ≥ 6.5% **Conditions where HbA1c may not be used for diagnosis:** ◦ Haemoglobinopathies ◦ Haemolytic anaemia ◦ Untreated iron deficiency anaemia ◦ Suspected gestational diabetes ◦ Children ◦ HIV ◦ CKD **To convert HbA1c into mmol/L= average plasma glucose = (2 * HbA1c) - 4.5** **To convert mmol/L into mg/dL= multiply it with 18**
Diabetes UK guidelines	• Diabetes UK suggests people with **IFG** should then be offered an **OGTT** to rule out a diagnosis of diabetes, also used for gestational diabetes • OGTT ◦ Preparation before test: ▪ Unrestricted carbohydrate diet for 3 days ▪ Overnight fasting for at least 8 hours ▪ Sampling: plasma glucose is measured before and 2 hours after 75g oral glucose drink

	Normal	Impaired Glucose tolerance	DM
Fasting	<7mmol/L (<126mg/dL)	<7mmol/L (<126mg/dL)	≥7mmol/L (≥126mg/dL)
2 hours after glucose	<7.8 mmol/L (<140mg/dL)	7.8--11 mmol/L (140--199mg/dL)	≥11.1 mmol/L (≥200mg/dL

- **Management of Impaired glucose tolerance test:**
  - lifestyle modification: weight loss, increased exercise, change in diet
  - at least **yearly** follow-up with blood tests is recommended
  - **NICE recommend metformin for adults at high risk** 'whose blood glucose measure (fasting plasma glucose or HbA1c 6.0-6.4) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme'

Complications

Diabetic retinopathy	• Hyperglycemia increases retinal blood flow and metabolism which leads to chronic retinal hypoxiastimulates production of growth factors causing new vessels formation and increased vascular permeability Classification: **Non-Proliferative Retinopathy**

Mild NPDR	Moderate NPDR	Severe NPDR (4-2-1 rule)
• 1 or more microaneurysm	• Microaneurysm • Blot haemorrhages • Hard exudates • Cotton wool spots Venous bleeding/intra-arterial microvascular abnormalities less severe than in severe NPDR	• Blot haemorrhages and microaneurysm in **4 quadrants** • venous beading in at least **2 quadrants** • IRMA in at least 1 quadrant

Proliferative Retinopathy:

- Retinal neovascularisation - may lead to vitreous haemorrhage
  Fibrous tissue forming anterior to retinal disc
  More common in Type I DM, 50% blind in 5 years

Maculopathy	• **Hard exudates**, macular haemorrhage • Rx: photocoagulation
Eye	• Cataract
Nephropathy	• All patients should be checked annually • Albumin: Creatinine ratio (ACR) in early morning specimen • ACR > 2.5 in male, > 3.5 in female = microalbuminuria • Rx: ACE or ARB
Neuropathy	• Weakness., wasting and paraesthesia, Carpal tunnel syndrome • Treatment: amitriptyline, duloxetine, gabapentin or pregabalin

Classification

Type	Type-1 diabetes	Type-2 Diabetes
	• Also known as insulin dependent diabetes mellitus (IDDM)	• Also known as Non-insulin dependent diabetes mellitus (NIDDM)
Cause	• Autoimmune destruction of β cells	• ↓↑ resistance to insulin, progressive pancreatic • β-cell failure
Epidemiology	• Younger patients usually < 30 years • Usually lean	• Older patients usually > 30 years • Usually overweight
Genetics	• Family history uncommon • HLA DR3 and HLA DR4 association • 30-50% concordance rate in identical in identical twins	• Family history common • No HLA association • >90% accordance rate in identical twins

Maturity-onset diabetes mellitus of the young (MODY)

- This autosomal dominant syndrome is characterized by mild hyperglycemia and hyposecretion of insulin but no loss of beta cells.
- It has an earlier onset (typical age < **25 years old)** than type 2 diabetes mellitus.
- It is caused by a diverse group of single gene defects. Such as **glucokinase gene (MODY 2), HNF-1 alpha gene (MODY 3 most common)**

Secondary Diabetes Mellitus

Hereditary hemochromatosis	**Mnemonic ABCDH** • *Arthralgia, Bronze skin, Cardiomyopathy, Cirrhosis of liver, Diabetes (pancreatic damage), Hypogonadism (anterior pituitary damage)* ***Bronze diabetes*** Characteristics include excess iron absorption and parenchymal deposition of hemosiderin, with reactive fibrosis in various organs, especially the pancreas, liver, and heart
Carcinoma of the pancreas	• Diabetes mellitus may be the presenting sign.
Cushing syndrome	• Produces hyperglycemia as a result of increased gluconeogenesis and impaired peripheral utilization of glucose
Acromegaly	• Produces hyperglycemia due to the anti-insulin like effect of growth hormone.
Pregnancy	• Pregnancy may be associated with transient diabetes mellitus (gestational diabetes). • Diabetes mellitus is characteristically associated with increased fetal birth weight and increased fetal mortality, notably from neonatal respiratory distress syndrome (hyaline membrane disease).

Multiple Endocrine Neoplasia (MEN) Syndrome

- MEN is inherited as an autosomal dominant
- The table below summarises the three main types of multiple endocrine neoplasia

MEN-I (Wermer syndrome)	MEN-IIa (Sipple syndrome)	MEN-IIb (MEN III)
• **3P'S** includes hyperplasia or tumors of the ◦ *Pituitary* ◦ *Parathyroid, or* ◦ *Pancreatic islets* • In addition, it may include hyperplasias or tumors of the thyroid or adrenal cortex.	• *Medullary thyroid cancer* (70%) • **2P's** ◦ Phaeochromocytoma Parathyroid (60%)	• *Medullary carcinoma* • *Multiple mucocutaneous neuromas or ganglioneuromas.* • **1P's** ◦ Pheochromocytoma,
• It is linked to mutations in the ***MEN I* gene**	• It is linked to mutations in the ***ret*** oncogene	• It is linked to mutations in the ***ret*** oncogene
• Most common presentation = hypercalcaemia	• Note: when a diagnosis of pheochromocytoma is made, the finding of characteristic *ret* mutations would justify prophylactic thyroidectomy (because of the danger of fatal medullary carcinoma of the thyroid).	• In contrast to MEN IIa, it does not induce hyperparathyroidism. • It is linked to different mutations in the *ret* oncogene compared with MEN IIa.

Neuroendocrine Tumors

- Heterogeneous group of neoplasms originating from neuroendocrine cells (which has traits similar to nerve cells and hormone-producing cells).

Carcinoid Tumors	• Neuroendocrine tumors When metastatic to the liver, can lead to carcinoid syndrome;
	• This syndrome is: Caused by the elaboration of vasoactive peptides and amines, especially serotonin
	• Manifest clinically by:
	  ◦ Cutaneous flushing
	  ◦ Watery diarrhea and abdominal cramps
	  ◦ Bronchospasm
	  ◦ Valvular lesions of the right side of the heart
	• Carcinoid tumors most commonly arise in small intestine and lung.

Insulinoma	• Tumor of pancreatic β cells characterized by overproduction of insulin leading to hypoglycaemia Clinical characteristics include the Whipple triad:
	  ◦ *Episodic hyperinsulinemia and hypoglycemia*
	  ◦ Central nervous system (CNS) dysfunction temporally related to hypoglycemia (confusion, anxiety, stupor, convulsions, coma)
	  ◦ Dramatic reversal of CNS abnormalities by glucose administration
	• To differentiate between endogenous insulin production from exogenous insulin
	  ◦ *Circulating C-peptide is characteristically increased in patients with insulinoma.*
	  ◦ *In contrast, C-peptide is not increased by exogenous insulin administration because it is removed during the purification of commercial insulin preparations*
	• Treatment:
	  ◦ Surgical resection.

Glucagonoma	• Tumor of pancreatic α cells resulting in overproduction of glucagon casuing secondary diabetes mellitus
	• Clinical features---Mnemonic **5D**'s
	  ◦ ***D****ermatitis (necrolytic migratory erythema)*, **D**iabetes (Hyperglycemia), **D**VT, **D**eclining weight, **D**epression.
	• Treatment:
	  ◦ Octreotide & surgery

Gastrinoma	• This tumor is often malignant and sometimes occurs in extrapancreatic sites. • It results in gastrin hypersecretion and hypergastrinemia. • It is associated with the **Zollinger-Ellison syndrome** (marked gastric hypersecretion of hydrochloric acid, recurrent peptic ulcer disease, and hypergastrinemia)
VIPoma	• A rare tumor. • This endocrine tumor is marked by secretion of vasoactive intestinal peptide (VIP). • It is associated with **W**atery **D**iarrhea, **H**ypokalemia, and **A**chlorhydria (**WDHA**) syndrome. • Also known as Verner-Morrison syndrome or pancreatic cholera.

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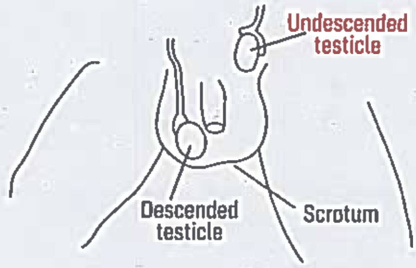
Chapter 8: Reproduction

Diseases of the Testes

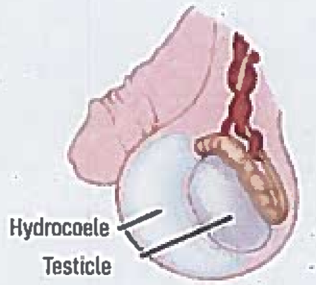
Cryptorchidism

- Developmental failure of a testis to descend into the scrotum.
- This condition is associated, with increased incidence of germ cell tumors, especially seminoma and embryonal carcinoma.



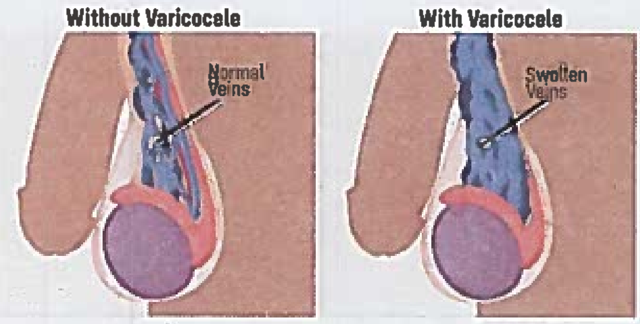
Hydrocele

- Is serous fluid filling and distending the tunica vaginalis.
- Congenital hydrocele: due to incomplete obliteration of processus vaginalis
- Acquired hydrocele: secondary to infection or to lymphatic blockage by tumor.
- *Transillumination→positive*



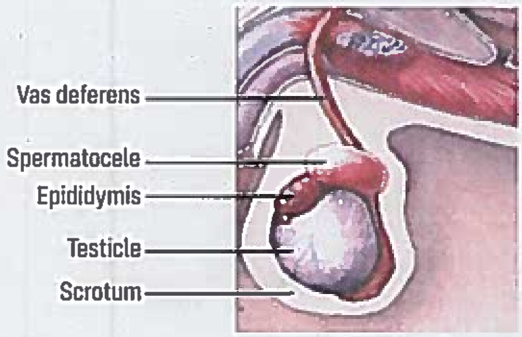
Varicocele

- Dilated veins in pampiniform plexus due to↑venous pressure.
- Most often on left side because of↑resistance to flow from left gonadal vein drainage into left renal vein
- Can cause infertility
- *Transillumination→negative*
- *On palpation→bag of worms*



Spermatocele

- Is a sperm-containing cyst.
- Due to dilated epididymal duct or rete testis

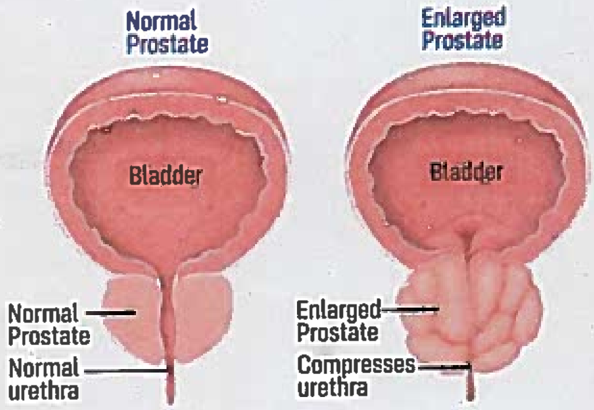


Diseases of the Prostate

- Chestnut-shaped located at the base of the bladder. It comprises of four groupings of glands, periurethral, transitional, central, and peripheral zones.
- *The periurethral, transitional, and central zones collectively are equivalent to the older designation of anterior, middle, and lateral lobes and are often the site of benign prostatic hyperplasia (BPH).*
- *The peripheral zone is equivalent to the older designation of posterior lobe; it is the characteristic site for carcinoma.*

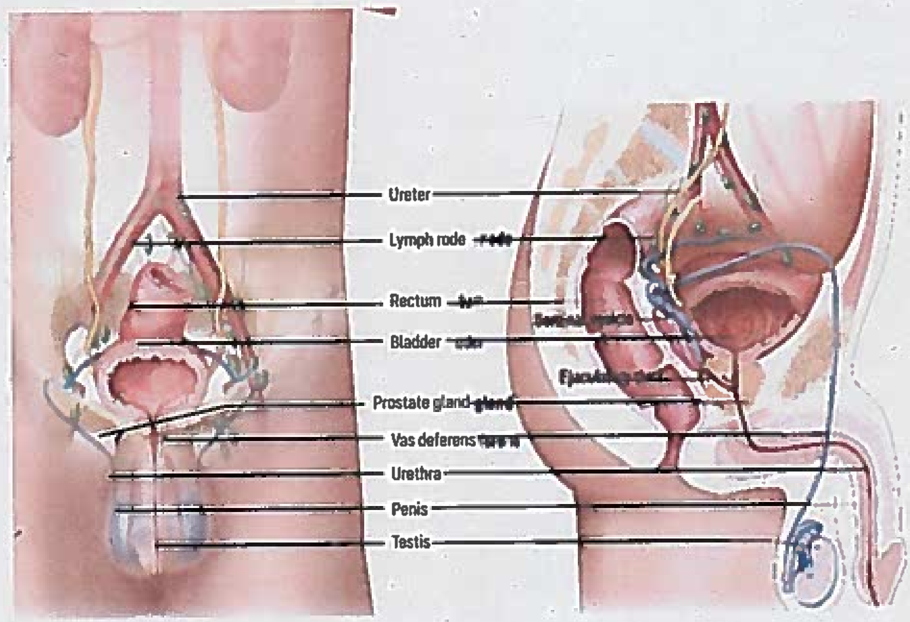
Benign Prostatic Hyperplasia

- Common in men > 50 years old.
- Although BPH has no relation to prostate cancer, the two conditions can coexist
- Characterized by smooth, elastic, firm nodular enlargement (hyperplasia not hypertrophy) of periurethral (lateral and middle) lobes, which compress the urethra into a vertical slit.
- *↑free form PSA*
- Clinical features:
    - Frequency, dysuria, hesitancy (difficulty in starting urination)
    - Urinary tract infection, hydronephrosis
    - Incomplete bladder emptying
- Treatment:
    - α1-antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle
    - 5α-reductase inhibitors (e.g., finasteride)
    - PDE-5 inhibitors (e.g., tadalafil)
    - Surgical resection (e.g., TURP, ablation)



Prostatic Adenocarcinoma

- Common in men > 50 years old.
- *Arises most often from posterior lobe (peripheral zone) of prostate*
- *↑total PSA; with↓ fraction of free PSA*
- *↑prostatic acid phosphatase (PAP).*
- *↑ALP (reflects metastasis to bone—Osteoblastic activity)*



Testicular Tumors

Testicular germ cell tumors (95%)	Seminoma	• This tumor is analogous to dysgerminoma, a tumor of the ovary • *It is the most common testicular germ cell tumor.* • Painless enlargement of the testis. • Seminomas *are very radiosensitive* and can often be cured, even when there are metastases to abdominal lymph nodes. • *Excellent prognosis* • Findings→ ↓*placental ALP,* ↑*hCG, Fried egg appearance.*
	Embryonal carcinoma	• This tumor is analogous to a similar tumor occurring in the ovary. • *Early metastasis and worse prognosis than seminoma* • Findings→ ↓*hCG*
	Yolk sac (endodermal sinus) tumor	• This tumor is analogous to endodermal sinus tumor of the ovary. • *Most common testicular tumor in boys < 3 years old.* • ↑*AFP* • *The classic finding is the Schiller-Duval body.*
	Teratoma	• This germ cell tumor is derived from two or more embryonic layers • Malignant in adults. Benign in children
	Choriocarcinoma	• This tumor is analogous to Choriocarcinoma of the ovary. • *Histologically resemble placental syncytiotrophoblasts and cytotrophoblasts.* • ↑ hCG • *Highly chemosensitive.*
Testicular non-germ cell tumors (5%)- (stromal tumors	Leydig cell tumor	• This tumor is similar to the Sertoli-Leydig cell tumor of the ovary. • It is most often benign. • It is often characterized by intracytoplasmic Reinke crystals. • ↑*Androgen and estrogen.* • The tumor is most often associated with precocious puberty in children and with gynecomastia in adults
	Sertoli cell tumor (andrioblastoma)	• This tumor is also similar to the Sertoli-Leydig cell tumor of the ovary.

Ovarian Tumors

Surface Epithelial Stromal Tumors	Serous tumor	• *Most common ovarian neoplasm.* • Lined with fallopian tube-like epithelium. • Often bilateral • *Psammoma bodies present*
	Mucinous tumors	• Multiloculated, large. Lined by mucus-secreting epithelium • *No Psammoma bodies but extend to peritoneum forming psuedomyxoma peritonei.*
	Endometroid	• Endometriosis (ectopic endometrium-like tissue) within ovary with cyst formation • "Chocolate cyst"—endometrioma filled with dark, reddish-brown blood
	Clear cell adenocarcinoma	• They are the most common ovarian tumors seen in association with endometriosis,
	Brenner tumor	• They are characterized by small islands of epithelial cells resembling Bladder transitional epithelium interspersed within a fibrous stroma.

Germ Cell Tumors	Dysgerminoma	• Analogous to testicular seminoma.
	Yolk sac (endodermal Sinus) tumor	• This tumor is analogous to endodermal sinus tumor of the testis. • *It produces AFP*
	Teratoma	• Tumors derived from two or three embryonic layers.
Sex Cord Stromal Tumors	Fibroma	• *It may be associated with Meigs syndrome, a triad of ovarian fibroma, ascites, and hydrothorax*
	Granulosa cell tumor	• *Estrogen-secreting tumor causes precocious puberty.* • *In adults, it is associated with endometrial hyperplasia or endometrial carcinoma.* • *Call-Exner bodies→important diagnostic feature*
	Sertoli-Leydig cell tumor	• *Androgen-secreting tumor is associated with Virilism (masculinization)*
Metastatic Tumor To Ovaries	Krukenberg tumor	• *GI malignancy (most often stomach) that metastasizes to ovaries→ mucin-secreting signet cell adenocarcinoma*

Breast

Fibrocystic disease	• Most common disorder of the breast.
	• It is uncommon before adolescence or after menopause.
	• Usually bilateral.
	• Disease is postulated to result from increased activity of estrogen or decrease progesterone activity.
	• Subtypes:
	  ◦ Nonproliferative forms (stromal fibrosis and cyst formation) are not associated with an increased risk of breast cancer.
	  ◦ Epithelial hyperplasia or sclerosing adenosis carries a slightly increased risk while the increased risk of cancer

Fibroadenoma	• *Most common breast tumor in women younger than 25 years of age.* • This tumor is entirely benign, painless and is not a precursor of breast cancer.
Phyllodes tumor	• Large mass of connective tissue and cysts with "leaf-like" lobulations

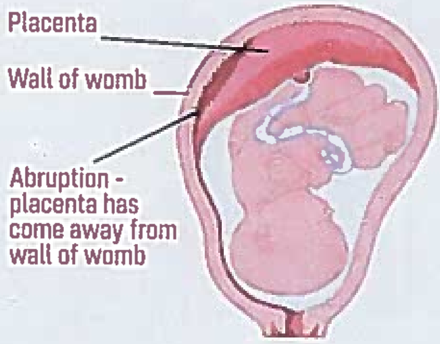
Gynecomastia	• *Breast enlargement in males due to↑estrogen compared with androgen activity.*
	Causes:
	  ◦ *Cirrhosis*
	  ◦ *Hypogonadism* (e.g., Klinefelter syndrome)
	  ◦ Testicular tumors
	  ◦ Drugs (Mnemonic: Some Hormones Create Knockers)
	    ▪ *Spironolactone, Hormones, Cimetidine, Ketoconazole.*

	• *Most common malignancy in females*
	• Risk factors→↑estrogen exposure, older age at 1st live birth, obesity, smoking *BRCA1 or BRCA2 gene mutations.* Early menarche and late menopause
	• *Occurs most frequently in the upper outer quadrant (50%) of the breast*
	• **Types:**
	  ◦ Non-invasive:
	    ▪ Ductal carcinoma in situ
	    ▪ Paget disease of the breast
	    ▪ lobular carcinoma of the breast

Breast carcinoma	• Invasive: • Invasive ductal carcinoma • Invasive lobular carcinoma • Medullary carcinoma • Mucinous carcinoma
	• Treatment: • Partial or radical mastectomy • Chemotherapy • Hormonal therapy: • *Tamoxifen (anti-estrogen drug)→given in pre-menopausal women* *Anastrazole (aromatase inhibitors)→given in post-menopausal women*

Disorders of Pregnancy

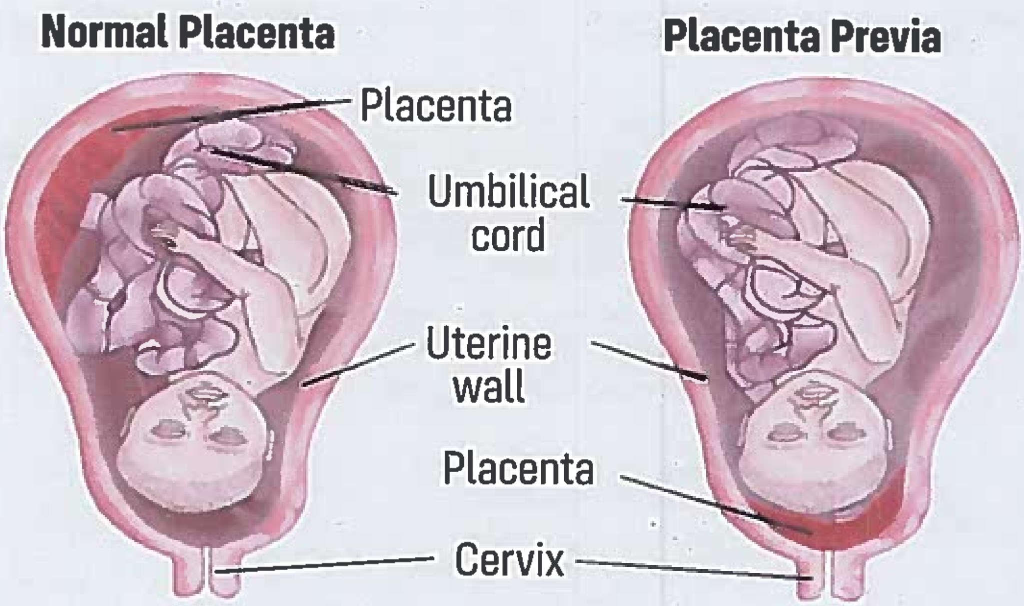
Abnormalities of Placental Attachment



- Placental abruption (abruptio placentae)
  - Premature separation (partial or complete) of the placenta.
  - *This is an important cause of antepartum bleeding and fetal death.*
  - *Risk factors: trauma (e.g., motor vehicle accident), smoking, hypertension, preeclampsia*
  - *It is often associated with disseminated intravascular coagulation (DIC)*

- Placenta accreta
  - *Defective decidual layer→abnormal attachment and separation after delivery*
  - *Risk factors: prior C-section, inflammation, placenta previa*
  - *It is manifested clinically by impaired placental separation after delivery, sometimes with massive hemorrhage.*

- Placenta previa
  - *Attachment of placenta to lower uterine segment over (or < 2 cm from) internal cervical os.*
  - *Risk factors: multiparity, prior C-section.*
  - *Associated with painless third trimester bleeding*



Disorders of Pregnancy (continued)

Ectopic pregnancy

- Defined as implantation of conceptus outside the uterine cavity
- Common site
  - *Ectopic pregnancy occurs in the fallopian tube in over 95% of cases.*
  - *The most common location in the fallopian tube for ectopic pregnancies to occur is the ampulla (70.0%)*
- Risk factors:
  - Previous ectopic pregnancy
  - History of infertility
  - Previous PID
  - Previous tubal surgery
- Clinical features
  - *Classic triad of amenorrhea, vaginal bleeding, and abdominal pain*
  - *Clinically mistaken for appendicitis.*

Gestational Trophoblastic Disease

- Includes disorders characterized by degenerative or neoplastic changes of trophoblastic tissue.

1. Hydatiform mole

- Characterized by cystic swelling of chorionic villi, accompanied by variable trophoblastic proliferation
- Presentation→*enlarged uterus, vaginal bleeding, ↑hCG*
- Treatment→dilatation and curettage , methotrexate
- Two types

	Complete Mole	Partial Mole
Karyotype	• *46,XX; 46,XY*	• *69,XXX; 69,XXY; 69,XYY*
Fetal Parts	• No	• Yes
Imaging	• "Honeycombed" uterus or "clusters of grapes", *"snowstorm" appearance on ultrasound*	• Fetal parts
Risk Of Choriocarcinoma	• 2%	• Rare

1. Gestational Choriocarcinoma

- Aggressive malignant neoplasm that occurs more frequently than ovarian choriocarcinoma.
- An increased serum concentration of hCG is an important diagnostic sign.
- Characteristics include early hematogenous spread to the lungs
- No chorionic villi present
- Presents with abnormal*↑β-hCG, shortness of breath, hemoptysis. Hematogenous spread to lungs "cannonball"→ appearance*

Hypertension In Pregnancy

Chronic Hypertension or pre-existing HTN	• It refers to BP> 140/90 before the start of pregnancy or before 20 weeks gestation

Pregnancy Induced Hypertension	• Also known as gestation hypertension
	• It refers to HTN occurring after 20 weeks of gestation in the absence of proteinuria
	• HTN in pregnancy is defined as
	  · Systolic >140mmHg or diastolic >90mmHg
	OR
	  · Increase above booking reading of >30mmHg systolic or >15mmHg diastolic
	• Treatment: Antihypertensives (Hydralazine, α-Methyldopa, ***Labetalol (FIRST CHOICE)***, Nifedipine

Pre-Eclampsia	• *It refers to pregnancy induced HTN in the presence of 300mg protein in 24 hour urine collection*
	• Nice guidelines:
	  ◦ **Women who are at high risk of developing pre-eclampsia should take aspirin 75mg – OD from 12 weeks until the birth of baby**
	  ◦ High risk group patients include:
	    ▪ HTN during previous pregnancy
	    ▪ CKD, DM
	    ▪ Autoimmune disorders such as SLE or Anti-phospholipid syndrome

Eclampsia	• *Defined as grand mal convulsion occurring in a woman with established pre-eclampsia, in the absence of any other neurological or metabolic cause* • Treatment: IV magnesium sulfate, antihypertensives, immediate delivery.
HELLP syndrome	• *It is combination of **Hemolysis, Elevated Liver enzymes, and Low Platelets*** • A manifestation of severe preeclampsia • Treatment: Immediate delivery.

Chapter 9: Musculoskeletal System

Cell Biology of Bone

Osteoblast	• Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP • Differentiates from mesenchymal stem cells in periosteum
Osteoclast	• Dissolves bone by secreting H+ and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors.

Diseases of Skeletal Muscle

Muscular Dystrophies

Osteoblast	• Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP • Differentiates from mesenchymal stem cells in periosteum
Becker muscular dystrophy	• X-linked disorder typically due to non-frameshift deletions in dystrophin gene (partially functional instead of deleted). • Less severe than Duchenne
Myotonic dystrophy	• Autosomal dominant • Trinucleotide repeat disorder : **CTG** (You **SEE** **T**onic **G**estures) • Characteristics include a weakness associated with myotonia (inability to relax muscles once contracted). • Associated features **C**ataracts, **T**oupee (early balding in men), **G**onadal atrophy

Myasthenia Gravis Vs. Lambert-Eaton Syndrome

	Myasthenia Gravis	Lambert-Eaton Syndrome
Frequency	Most common NMJ disorder	Uncommon
Pathophysiology	*Autoantibodies to postsynaptic ACh receptor*	*Autoantibodies to presynaptic Ca2+ channel →↓ACh release*
Clinical	Ptosis, diplopia, weakness Worsens with muscle use and recovery on rest. *Improvement after edrophonium (Tensilon) test*	Proximal muscle weakness, autonomic symptoms (dry mouth, impotence) Improves with muscle use
Associated With	Thymoma, Thymic hyperplasia	Small cell lung cancer
AChE Inhibitor Administration	Reverses symptoms (edrophonium to diagnose, pyridostigmine to treat)	Minimal effect

Diseases of Bone

Metabolic Bone Diseases

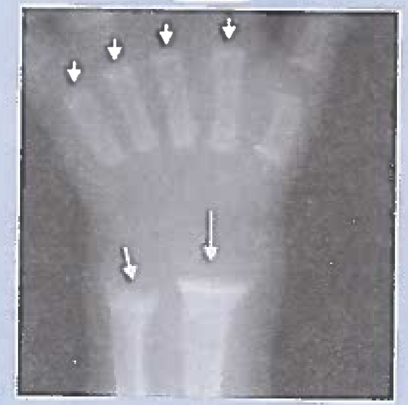
Osteoporosis

- Characterized by a decrease in bone mass
- *Normal bone mineralization and lab values (serum Ca_2+ and PO_4-)*
- Cause may be impaired synthesis or increased resorption of bone matrix protein because of
  - *Postmenopausal state* (estrogen deficiency is a presumptive cause)
  - Physical inactivity
  - Hypercorticism
  - Hyperthyroidism
  - Calcium deficiency
  - Can be secondary to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy)
- *It results in bone structures inadequate for weight bearing can lead to vertebral compression fractures*
- Diagnosed by a DEXA scan

Osteomalacia

- Vitamin D deficiency in adults.
- Defective calcification of osteoid matrix is characteristic.
- When secondary to renal disease, Osteomalacia is called renal osteodystrpphy

Rickets

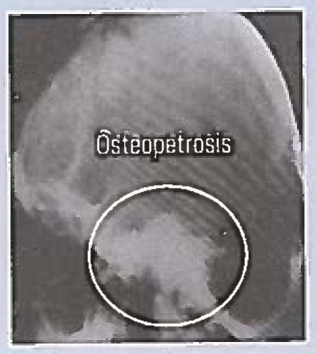


- Vitamin D deficiency in childrens.
- Defective calcification of osteoid matrix is characteristic.
- Clinical manifestations include:
  - Craniotabes(soft skull)→thinning and softening of occipital and parietal bones
  - *Rachitic rosary*: thickening of the Costochondral junctions that results in a string of-beads-like appearance
  - *Pigeon chest*→caused by protrusion of the sternum
  - *Bow legs (genu varum)*

    Widening and metaphyseal cupping/fraying in rickets.

Paget disease of bone (osteitis deformans

- Disorder of bone remodeling caused by ↑ osteoclastic activity followed by↑osteoblastic activity that forms poor-quality bone and mosaic pattern
- Complications:
  - Bone pain resulting from fractures: although bone is thick, it lacks strength; fractures can lead to deformity.
  - High-output cardiac failure can result from multiple functional arteriovenous shunts within highly vascular early lesions.
  - Hearing loss is caused by narrowing of the auditory foramen or direct involvement of the bones of the middle ear.
  - Osteosarcoma occurs in approximately 1% of cases

Osteopetrosis (marble bone disease, Albers-Schönberg disease) 	• Failure of normal bone resorption due to defective osteoclasts→ thickened, dense bones that are prone to fracture. • vimpair ability of osteoclast to generate acidic environment necessary for bone resorption • Defective osteoclasts cause overgrowth and sclerosis of cortical bone vit is associated with anemia as a result of decreased marrow space, and with blindness, deafness, and cranial nerve involvement because of narrowing and impingement of neural foramina • X-rays→show diffuse symmetric skeletal sclerosis (bone-in-bone, "stone bone"). • Bone marrow transplant is curative

Achondroplasia

- Most common cause of dwarfism.
- *Autosomal dominant disorder* is caused by a mutation in the fibroblast growth factor receptor 3 (FGFR3) gene
- Short limbs with a normal-sized head and trunk are characteristic (large head relative to limbs)
- Membranous ossification is affected

Osteitis Fibrosa Cystica (Von Recklinghausen Disease Of Bone)

- The cause is primary or secondary hyperparathyroidism.
- Widespread Osteolytic lesions are characteristic. *Cystic bone spaces filled with brown fibrous tissue ("brown tumor")*
- Brown discoloration resulting from hemorrhage with deposited hemosiderin

Lab Values in Bone Disorders

Disorder	Serum Ca2+	PO_4^{3-}	ALP	PTH	Notes
Osteoporosis	—	—	—	—	↓ bone mass
Osteopetrosis	—/↓	—	—	—	Ca2+↓in severe form
Paget disease of bone	—	—	↑	—	*Abnormal "mosaic" bone architecture*
Osteitis fibrosa cystica Primary hyperparathyroidism	↑	↓	↑	↑	"Brown tumours' Idiopathic or parathyroid hyperplasia, adenoma, carcinoma

Secondary hyperparathyroidism	↓	↑	↑	↑	*Often as compensation for CKD (↓ PO4 3- excretion and production of activated vitamin D)*
Osteomalacia/Rickets	↓	↓	↑	↑	Soft bones; vitamin D deficiency also causes 2° hyperparathyroidism

Bone Tumors

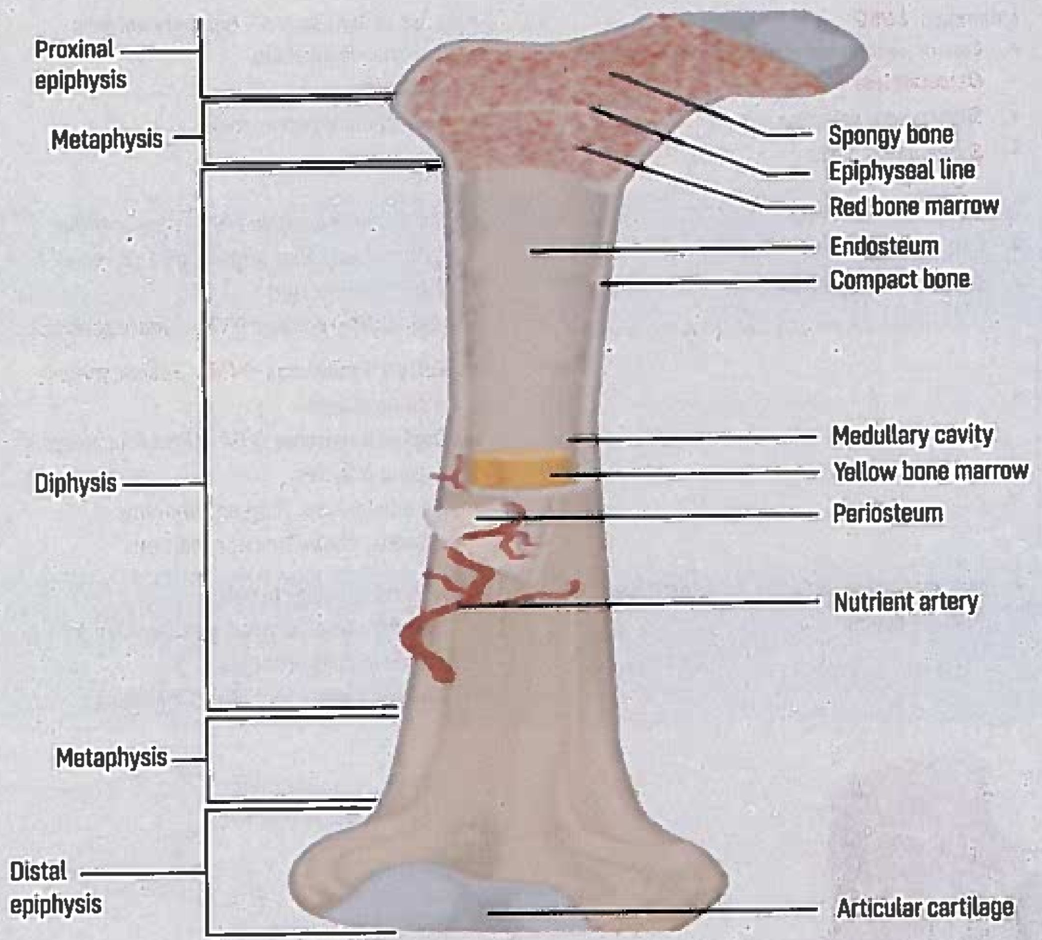
Remember **GEOMED** Mnemonic for location

- *Giant cell --- Epiphysis*
- *Osteosarcoma --- Metaphysis*
- *Ewing sarcoma --- Diaphysis*

Type	Epidemiology/Location	Epidemiology/Location
Benign Tumors		
Osteochondroma	• *Most common benign tumor of bone.* • Most frequently in men younger than 25 years of age. • *Most often originates from the metaphysis of long bones, with the lower end of the femur or the upper end of the tibia being favored locations*	• Bone growth is covered by a cap of cartilage projecting from the surface of a bone (exostosis) • Transformation to Chondrosarcoma is rare
Giant cell tumor	• Peak incidence→20-40 years Tumor occurs most often on the epiphyseal end of long bones; more than 50% occur around the knee.	• *X-ray "Soap bubble" appearance*
Malignant Tumors		

Osteosarcoma	• *Most common primary malignant tumor of bone*
	• *Tumor occurs most frequently in the metaphysis of long bones;* the proximal portion of the tibia and most distal portion of the femur (around the knee) are preferred sites.
		• X-ray Codman triangle (from elevation of periosteum) Or sunburst pattern
		• Predisposing factors
		  ◦ Paget disease of bone, chondroma,
		  ◦ Ionizing radiation Familial retinoblastoma

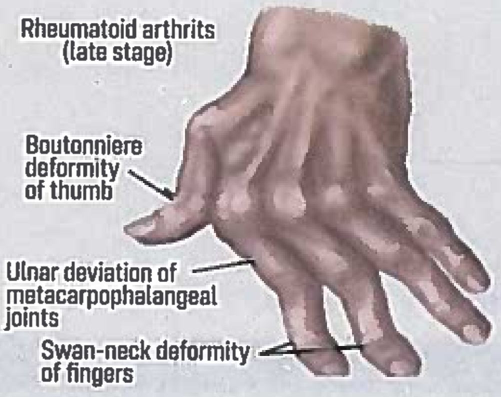
Ewing sarcoma	• Peak incidence→Boys < 15 years old. • Commonly appears in diaphysis of long bones, pelvis, scapula, ribs.	• *"Small blue cell" malignant tumor* • **11; 22 chromosomal translocation.** • Mnemonic: **11 + 22 = 33** (Patrick **Ewing**'s jersey number).

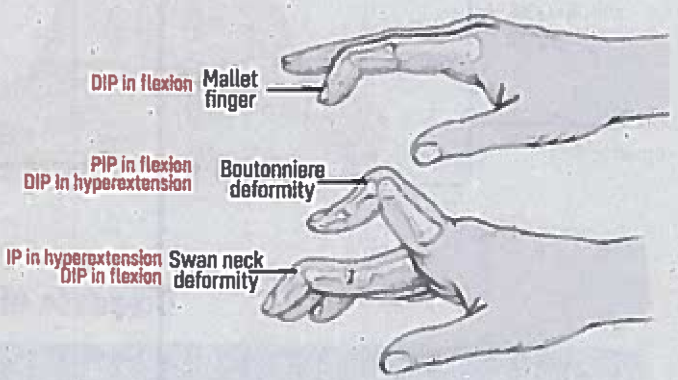


Diseases of Joints

	Osteoarthritis	Rheumatoid arthritis
Pathogenesis	• Noninflammatory joint disease is characterized by degeneration of articular cartilage • Osteoarthritis is most often related to mechanical trauma to the affected joints ("wear and- tear" arthritis)	• Chronic inflammatory disorder primarily affects the synovial joints • *Autoimmune disorder and Associated with HLA-DR4 (4 walls in a **rheum** (room)*
Presentation	• Asymmetric joint involvement. • **Morning stiffness of <15 minutes** • Improving with rest. • Pain in weight-bearing joints after use • Knee cartilage loss begins medially ("bowlegged").	• Symmetric joint involvement • **Morning stiffness of > 1 hour** • Improving with activity • Systemic symptoms (fever, fatigue, weight loss).
Joint Findings	• *Heberden's nodes*→prominent osteophytes at DIP joints • *Bouchards nodes*→prominent osteophytes at PIP joints • **Involves DIP and PIP, but not MCP**	• *Swan-Neck deformity* • *Boutonniere deformity* • Cervical joint involvement ost commonly C1,C2 **always perform X-ray cervical spine before ETT** • **Involves MCP, PIP, wrist; not DIP** • *Ulnar deviation of fingers*

Radiographic Hallmarks	*Mnemonic:* ***LOSS*** • *Loss of joint space--* ***typically non-uniform*** • ***Osteophytes*** • *Subarticular sclerosis* • *Subchondral cysts*	• *Loss of joint space--* ***typically uniform*** • *Soft tissue swelling* • ***Erosions*** • *Periarticular osteopenia*
Lab Findings	• RA factor→negative • ESR, CRP→normal • Anti-CCP→negative	• *RA factor→positive (70%- non-specific, IgM antibody that targets IgG Fc region)* • ESR, CRP→raised • *Anti-CCP→positive (90% --more specific)*
Extra articular manifestations		• **Felty's Syndromes**→*RA + Splenomegaly + Neutropenia* • **Caplan Syndrome**→*RA + Pneumoconisasis + Lung Nodules* • AA amyloidosis, Sjögren syndrome, scleritis, *carpal tunnel syndrome.*
Treatment	• Acetaminophen, NSAIDs, intra-articular glucocorticoids.	• NSAIDs, glucocorticoids, • **DMARD's** (methotrexate, sulfasalazine, hydroxychloroquine) • **Biologic agents** (eg, TNF-α inhibitors).





Some Other Features of Rheumatoid Arthritis and Management

Poor Prognostic Features	• Rheumatoid factor positive, Anti-CCP antibodies, HLA DR4, Poor functional status at presentation • X-ray: early erosions (e.g. after < 2 years) • Extra articular features e.g. nodules • Insidious onset & Female gender is associated with a poor prognosis.
Other Conditions Associated with A Positive RF	• Sjogren's syndrome (around 100%), Felty's syndrome (around 100%), Cryoglobulinemia II & III 40-100%, Infective endocarditis (= 50%), SLE (= 20-30%), Systemic sclerosis (= 30%)
Extra-Articular Complications with Rheumatoid Arthritis	• **Respiratory:** • Pulmonary fibrosis & nodules, pleural effusion, bronchiectasis (especially nonsmokers), bronchiolitis obliterans, complications of drug therapy e.g. methotrexate pneumonitis, infection (possibly atypical) secondary to immunosuppression • **Ocular:** • keratoconjunctivitis sicca (most common), episcleritis (erythema), scleritis (erythema and pain), keratitis, corneal ulceration, steroid-induced cataracts, chloroquine retinopathy

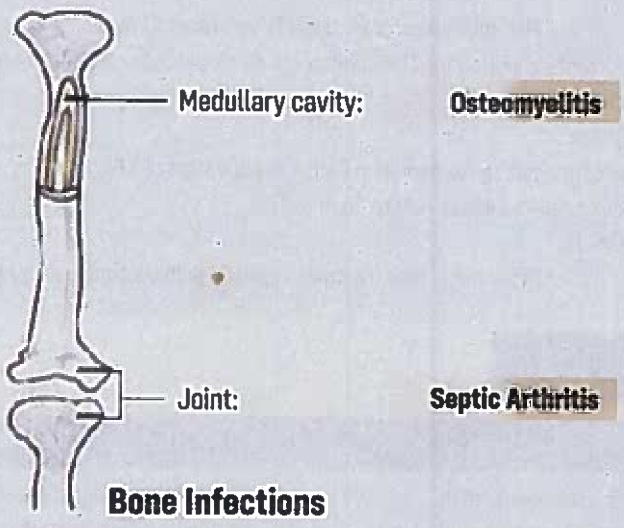
	• **Osteoporosis** • **Amyloidosis (AA)** • **Felty's syndrome** • RA + splenomegaly + low white cell count+ leg ulcer in chronic seropositive RA • Caplan's syndrome • RA + Pneumoconiosis + Lung Nodules
Management of Rheumatoid Arthritis	• **Initial therapy: (NICE guidelines 2009)** • Patients with newly diagnosed active RA start a combination of DMARDs (including methotrexate and at least one other DMARD), plus short-term glucocorticoids • **DMARDs:** • **Methotrexate** is the most widely used DMARD • Pregnancy • Women should avoid pregnancy for at least 3 months after treatment has stopped • BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment • Prescribing methotrexate: • Methotrexate is taken weekly, rather than daily • Check CBC, RFTs & LFTs before starting treatment and repeated weekly until therapy stabilized, thereafter patients should be monitored every 2-3 months • Folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose • The starting dose of methotrexate is 7.5 mg weekly (source: BNF) • Avoid prescribing trimethoprim or cotrimoxazole concurrently increases risk of marrow aplasia • Sulfasalazine • Leflunomide • Hydroxychloroquine • **TNF-inhibitors: (can cause Drug induced lupus)** • The current indication for TNF-inhibitor is an inadequate response to at least 2 DMARDs including methotrexate. • It includes • Etanercept: (can cause demyelination & reactivation of TB) • Infliximab (risks include reactivation of TB) • Rituximab: • Other important treatment options include analgesia, physiotherapy and surgery.

Gout vs. Pseudogout

Gout	Pseudogout
• Crystal deposition disease, characterized by deposition of *monosodium urate crystals* into joints and other tissues	• Crystal deposition disease, characterized by deposition of *calcium pyrophosphate deposition crystals* within articular cartilages
• Most common site→*1st metatarsophalangeal joint (podagra)*	• Most common site ankle
• Crystals→*needle like, negative birefringent*	• Crystals→*rhomboid shape, positive birefringent*
• Treatment • acute attack→NSAIDS, Colchicine, steroids • Chronic attack→*Allopurinol (should not be used in acute attack)*, Febuxostat	• Treatment • NSAIDS, Colchicine, steroids

Osteomyelitis and Septic arthritis

	Osteomyelitis	Septic arthritis
Definition	• Osteomyelitis is an infection of the bone. It normally affects the long bones of the body; however, it can affect any bone	• Septic arthritis is an infection of any joint and is an orthopaedic emergency. It most commonly affects the hip or knee joint, however it can affect any joint in the body
Features	• Subacute onset of limp / non-weight bearing / refusal to use limb • Localised pain and pain on movement • Tenderness • Soft tissue redness / swelling may not be present & may appear late +/- Fever	• Acute onset of limp / non-weight bearing / refusal to use limb • Pain on movement and at rest • Limited range / loss of movement • Soft tissue redness / swelling often present • Fever
Investigations	• **MRI is the imaging modality of choice**	• Urgent joint aspiration for synovial fluid microscopy and culture • Blood cultures
Organisms involved	• *Most common agent S→.aureus* • IV drug users→S. aureus • Neonates→H. influenza • ***Sickle cell disease→Salmonella***	• *S aureus (Most common)* • Streptococcus • Neisseria gonorrhoeae

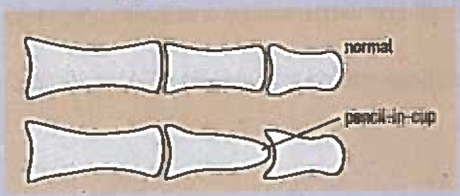


Bone Infections

Seronegative Spondyloarthritis (spondyloarthropathies)

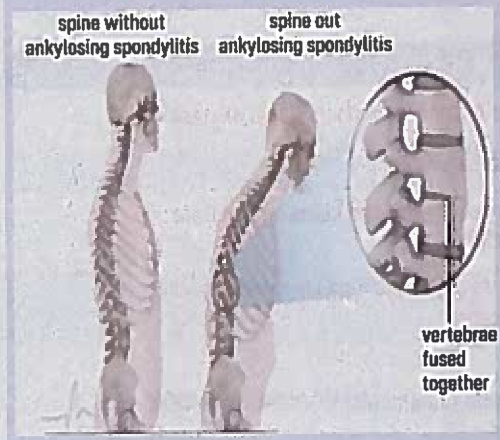
- Common features
  - Associated with HLA-B27
  - Rheumatoid factor negative - hence 'seronegative'
  - Peripheral arthritis, usually asymmetrical
  - Sacroiliitis
  - Enthesitis (inflamed insertion sites of tendons), e.g. Achilles tendonitis, plantar fasciitis
- Types: (mnemonic: PAIR)

Psoriatic Arthritis



- Occurs in approximately 10% of patients with psoriasis
- **Associated with skin psoriasis and nail lesions.**
- Asymmetric and patchy involvement
- Dactylitis and "pencil-in-cup" deformity of DIP on x-ray

Ankylosing Spondylitis



- *HLA-B27 association is most striking with this entity* (as many as 90% of patients)
- This chronic condition affects the spine and sacroiliac joints and can lead to rigidity and fixation of the spine as a result of bone fusion (ankylosis)---leading to *Bamboo spine (vertebral fusion)*
- Typically a young man who presents with lower back pain and stiffness
- Can cause restrictive lung disease due to limited chest wall expansion (costovertebral and costosternal ankylosis)
- Features: Mnemonic the A's---A for Ankylosing spondylitis
  - *Apical fibrosis* (CXR)
  - *Anterior uveitis*
  - *Aortic regurgitation*
  - Achilles tendonitis
  - AV node block
  - Amyloidosis

Inflammatory Bowel Disease

- Crohn disease and ulcerative colitis are often associated with spondyloarthritis.

Reactive Arthritis Or Reiter Syndrome.

- Classic triad: (Mnemonic: **Can't see, can't pee, can't bend my knee.**")
  - Conjunctivitis (Cant see)
  - Urethritis (cant pee)
  - Arthritis (cant bend my knee)
- Organisms responsible: (Mnemonic: **ShY ChiCS**)
  - Shigella
  - Yersinia
  - Chlamydi
  - Campylobacter
  - Salmonella.

Systemic Lupus Erythematosus (SLE)

- Most common connective tissue disorder, *more common in women's*
- It is multisystem inflammatory autoimmune disorder
- Classic scenario is like rash, joint pain, and fever, commonly in a female of reproductive age
- Two most important lesiosn frequently asked in exam:
  - Libman-Sacks Endocarditis— (Mnemonic: (LSE in SLE)
    - Nonbacterial, thrombi usually on mitral or aortic valve

    Lupus nephritis:
    - Glomerular deposition, can be nephritic or nephrotic
    - SLE Renal Complications WHO classification
      - Class I: normal kidney
      - Class II: mesangial glomerulonephritis
      - Class III: focal (and segmental) proliferative glomerulonephritis
      - *Class IV: diffuse proliferative glomerulonephritis--- most common and severe form.*
      - Class V: diffuse membranous glomerulonephritis
      - Class VI: sclerosing glomerulonephritis

- **SLE and Pregnancy:**
  - Unlike many autoimmune diseases systemic lupus erythematous (SLE) often becomes worse during pregnancy and the puerperium
  - *Neonatal complications include congenital heart block, it is strongly associated with **anti-Ro** (SSA) antibodies*
- **Common causes of death in SLE:**
  - Cardiovascular disease
  - Infections
  - Renal disease

- **Findings:**

Antinuclear antibodies (ANA)	Sensitive, not specific
Anti-dsDNA antibodies	*Highly specific, poor prognosis (renal disease)*
(Anti-Smith antibodies	*Specific, not prognostic*
Antihistone antibodies	*Sensitive for drug-induced lupus (eg, hydralazine, procainamide)*
↓C3, C4	*Formation of complexes leads to consumption of complement*

- **Diagnostic criteria (manifestation)Presence Of 4 Of Following 11 Criteria (mnemonic: DOPAMINe RASH)**

Discoid rash
Photosensitivity
Arthritis (non-erosive)
Malar rash **(butterfly rash on cheeks and nose with sparing of nasolabial folds)**
Immunological→positive anti-dsDNA (very specific, prognostic), anti-Sm (very specific, non prognostic), antiphospholipid antibodies
Neurological: seizures or psychosis
Renal: proteinuria, glomerulonephritis
ANA positive (Best screening test)
Serositis: Pericarditis, Pleuritis
Haematological: hemolytic anemia, lymphopenia, leukopenia, thrombocytopenia

- **Treatment:** NSAIDs, steroids, immunosuppressants, hydroxychloroquine.

Systemic Sclerosis

Introduction	• Systemic sclerosis is a generalized disorder of connective tissues of unknown etiology affecting skin, internal organs and vasculature.
	• More common in females
	• Definitions:
	  · Scleroderma= presence of tight, thickened skin.
	  · Systemic sclerosis= Scleroderma + internal organ involvement

Clinical features	• Skin:
	  · Tightening and thickenin of skin
	  · Mouse-like facies and purse string mouth
	  · *Sclerodactyly (claw-like appearance of the hand)*
	• Gastrointestinal

- *Dysphagia*, gastric outlet obstruction, erosive esophagitis
- Pulmonary (Major cause of mortality and morbidity):
  - Pulmonary HTN, pulmonary fibrosis
- Renal:
  - Hypertensive renal crisis—characterized by acute onset malignant HTN and renal failure
- Miscellaneus:
  - *Raynauds phenomenon,* Amenorrhea and infertitly

Types

- 2 major types

Limited cutaneous systemic sclerosis	Diffuse cutaneous systemic sclerosis
More common (70% cases)	Less common (30% cases)
Skin thickening on distal extremeities and face only	Skin thickening on distal extremeities, face and trunk
Pulmonary HTN>> Pulmonary Fibrosis	Pulmonary Fibrosis>> Pulmonary HTN
Prognosis good	Prognosis bad
Anti-centromere antibodies (60%)	Anti-scl-70 antibodies (30%)
CREST *syndrome: i.e.* • *Calcinosis.* • *Raynaud phenomenon* • *Esophageal dysmotility* • *Sclerodactyly* • *Telangiectasia*	Raynaud's phenomenon

Treatment

- NSAIDS, steroids
- Pulmonary fibrosis= cyclophosphamide
- Pulmonary HTN= bosentan (endothelin-1 antagonists)
- HTN renal crisis= ACE inhibitors

Inflammatory Myopathies (Polymyositis/Dermatomyositis)

Overview

- Inflammatory disorder causing symmetrical, proximal muscle weakness and characteristic skin lesions
- May be idiopathic or associated with connective tissue disorders or underlying malignancy (found in 20-25% - more if old patient)
- More common in females
- **Polymyositis is a variant of the disease where skin manifestations are not prominent**

Clinical features

- Dermatomyositis and polymyositits has the same clinical features except that skin is not involved in polymyositis
- Features –skin features only in dermatomyositis

Overview	- Photosensitive - Macular rash (similar to SLE) - Heliotrope rash (erythematous periorbital rash) - Gottron's papules - roughened red papules over extensor surfaces of fingers especially on knuckles - Shawl sign— (erythema of face, neck, shoulders and back) • Features similar to both dermatomyosistis and polymyositis - Proximal muscle weakness +/- tenderness - Raynaud's - Respiratory muscle weakness - Interstitial lung disease: e.g. Fibrosing alveolitis or organizing pneumonia - Dysphagia, dysphonia
Investigations (similar in both conditions)	• ↑ CK • ANA ⊕, • **anti-Jo-1** ⊕ • **anti-SRP (signal recognition peptide)** ⊕ • **anti-Mi-2 antibodies** ⊕. • **Muscle biopsy - most accurate investigation** • Screen for malignancy by U/S abdomen + pelvis-(♀)/+PSA (♂) – CT chest might be needed
Treatment	• Steroids followed by long-term immunosuppressant therapy (eg. methotrexate).

Sjögren Syndrome

Introduction	• Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates • Predominantly affects women 40–60 years old.
Clinical Manifestation	• Triad of - *Xerostomia (dry mouth),* - *Keratoconjunctivitis sicca (dry eyes), and one of several* - *Connective tissue or other autoimmune diseases, most often rheumatoid arthritis* • ***Sicca syndrome is a variant characterized by xerostomia and keratoconjunctivitis alone.*** • Involvement of salivary glands, *(bilaterally enlarged parotids)* • Involvement of lacrimal glands
Investigation	• ANA ⊕. • *Anti SS-A (anti-Ro) -----less specific* • *Anti SS-B (anti-La) -------Highly specific*

Extractable Nuclear Antigens:

- Specific nuclear antigens, usually associated with being ANA positive
- Examples:

anti-Ro	*Sjogren's syndrome, SLE, congenital heart block*
anti-La	*Sjogren's syndrome*
anti-Jo 1	*Polymyositis*
anti-scl-70	*Diffuse cutaneous systemic sclerosis*
anti-centromere	*Limited cutaneous systemic sclerosis*

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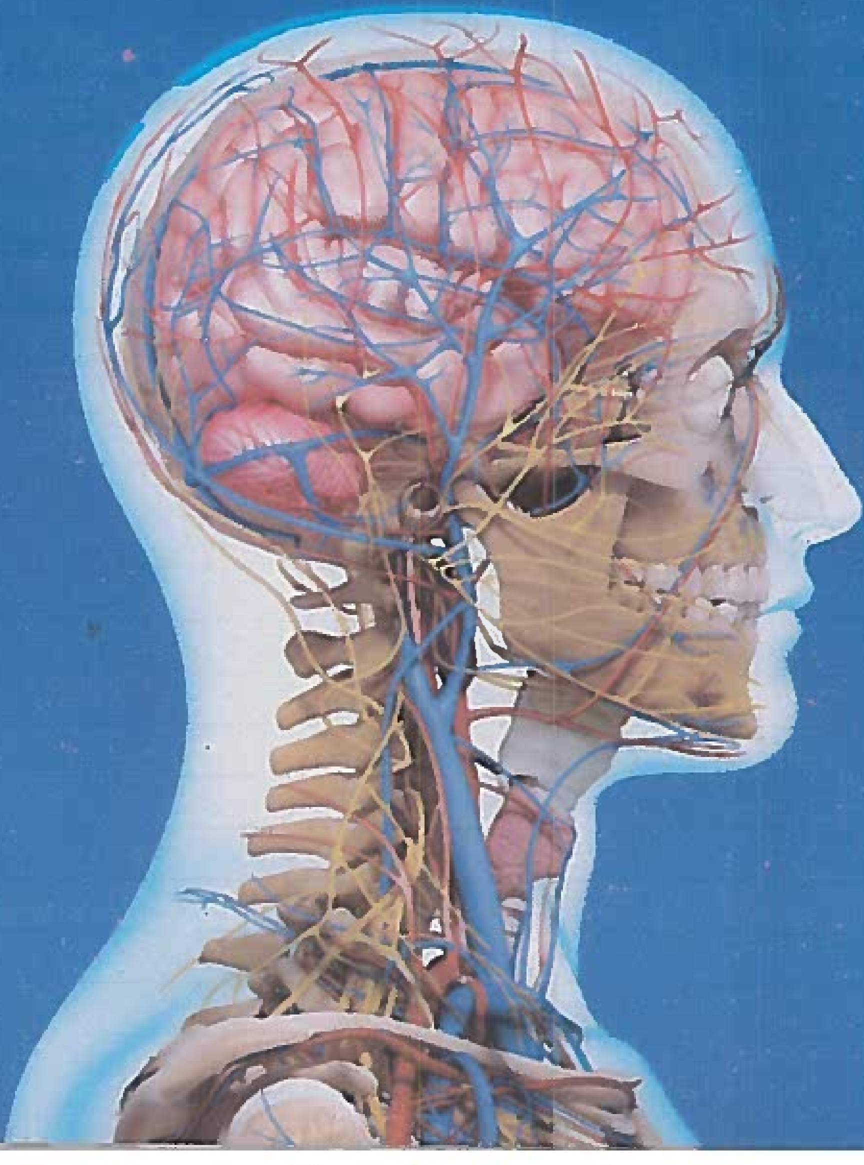
3

NEUROLOGY AND SPECIAL SENSES



Chapter 1: Head and Neck

SKULL

Bone Of Skull

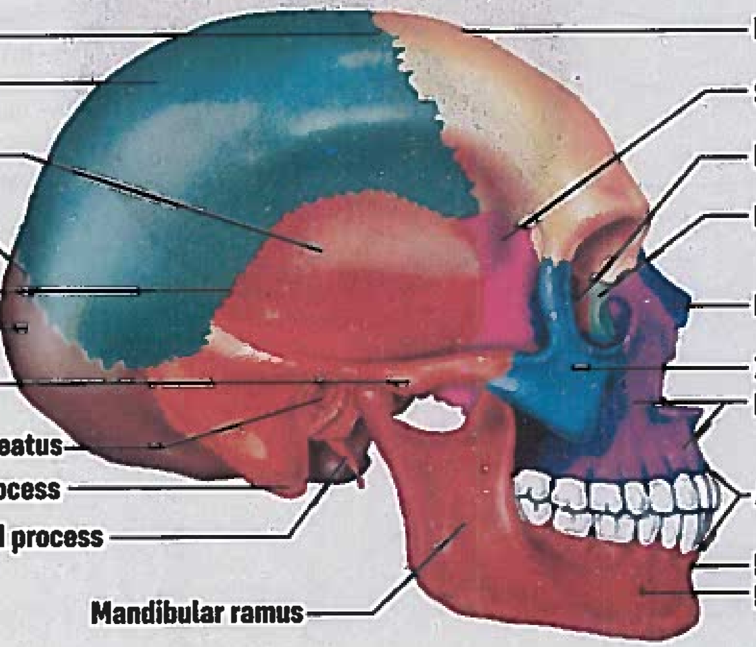
PAIRED	UNPAIRED
• Parietal	• Frontal
• Temporal	• Occipital
	• Ethmoid
• Mnemonic: PEST OF → Parietal, Ethmoid, Sphenoid, Temporal, Occipital, Frontal	• Sphenoid

Bones Of Facial Skeleton

PAIRED	UNPAIRED
• Maxilla	• Mandible
• Zygomatic	• Vomer
• NasaTempl	
• Lacrimal	
• Palatine	
• Inferior nasal concha	

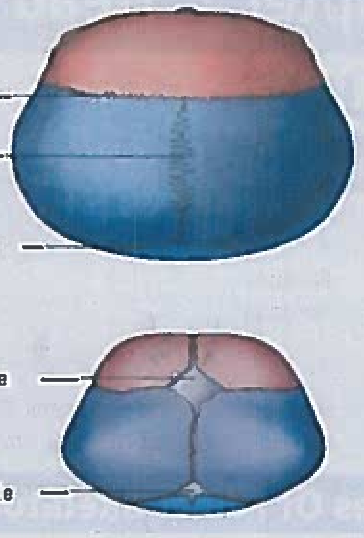
Skull Joints

- Immovable and fibrous in type known as sutures, with the exception of temporomandibular joint.



Fontanells

Anterior fontanelle	• Site of membranous gap in fetal skull, between coronal and sagittal suture (at bregma) • Closes at 18 months of age
Posterior fontanelle	• Site of membranous gap in fetal skull, between sagittal and lamboid suture (lambda) • Closes at 3 months of age



Foramens

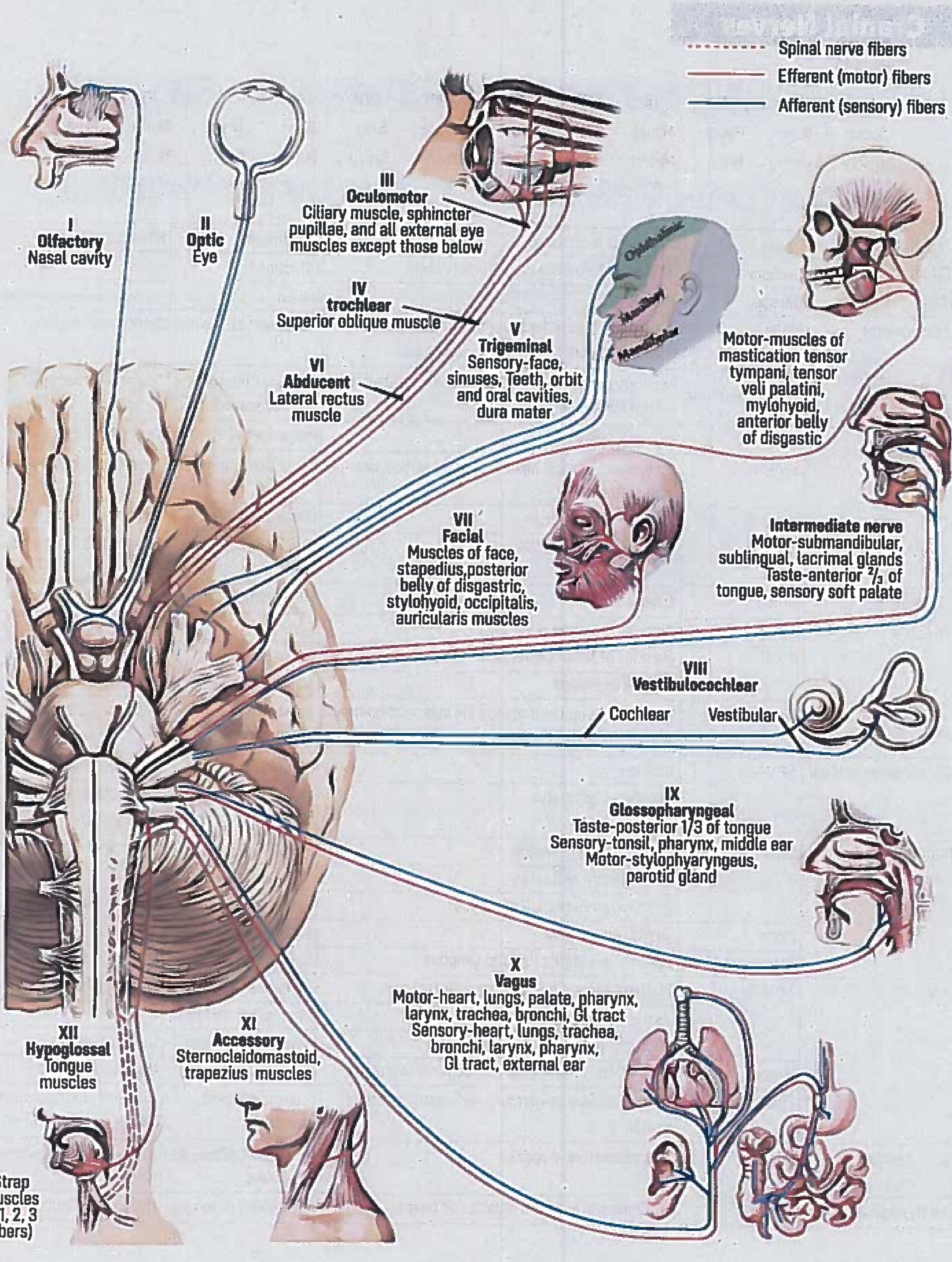
Note the location of foramens, structures passing through them are explained later in this chpater

Cranial Nerves

Mnemonic:

I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Some	Says	Marry	Money	But	My	Brother	Says	Big	Brains	Matter	Most
Sensory	Sensory	Motor	Motor	Both	Motor	Both	Sensory	Both	Both	Motor	Motor

Cranial Nerve	Fibres	Structures Innervated	Funchtions	Brainstem Nudeus
I Olfactory	Sensory	Olfactory epithelium (via olfactory bulb)	Olfaction	....
II Optic	Sensory	Retina	Vision	....
III Oculomotot	Motor	Superior/middle/inferior rectus, inferior oblique, levator plapebrae.	Movement of eye ball	Oculomotor nucleus
	Parasympathetic	Pupillary constrictor, ciliary muscle of eyeball. Both via the **ciliary ganglion**	Pupillay Constriction and accommodation	Oculomotor nucleus
IV Trochlear	Motor	Superior oblique	Movement of eye ball	Trochlear nucleus
V Trigeminal	Sensory	Face, scalp, cornea, nasal and oral cavities, cranial dura mater.	Generalsensation	Trigeminal Sensory nucleus
	Motor	Muscles of mastiction	Opening/closing mouth	Trigeminal Motor nucleus
		Tensor tympani muscle	Tension of tympanic membrane	Trigeminal Motor nucleus
VI Abdudcens	Motor	Lateral rectus	Movement of eyeball	Abducens nucleus
VII Facial	Sensory	Anterior 2/3 of tongue	Taste	Nucleus Solitarius
	Motor	Muscles of facial expression	Facial Movement	Facial Motor nucleus
		Stapedius Muscle	Tension of ossicles	Facial Motor nucleus
	Parasympathetic	Salivary and lacrimal glands **via submandibular and pterygopalatine ganglia**	Salivation and lacrimation	Superior Salivaroty Nucleus
VII Vestibulocochlear	Sensory	Cochlea	Hearing	Chochlear Nucleus
		Vestibular apparatus	Proriception of head, balance.	Vestibular nucleus
IX Glossopharyngeal	Sensory	Eustachian tube, middle ear	GeneralSensation,	Trigeminal Sensory nucleus
		Caroitd Body, and sinus	Chemo/baroreception	
		Pharynx, posterior 1/3 of tongue	Taste	Nucleus Solitarius
	Motor	Styropharyngeous	Swallowint	
	Parasympathetic	Salivary glands via the **otic ganglion**	Salivation	Inferior Salivatory nucleus
X Vagus	Sensory	Pharynx, larynx, oesophagus, external ear	General Sensation	Trigeminal Sensory nucleus
		Aortic bodies and arch	Chemo/barorecetion	
		Thoracic and abdominal viscera	Visceral Sensation	Nucleus Solitarus
	Motor	Soft Palate, larynx, pharynx, upper oesophagus	Speech,swallowing	Nucleus Ambiguus
	Parasympathetic	Cardiovascular, respiratory and gastrointestinal systems.	Control of these systems	Dorsal Motor nucleus of Vagus
XI Accessory	Motor	Sternomastoid, trapezius	Movement ofhead and shoulders	Nucelus Ambihuus,crinial nerves
XII Hypoglossal	Motor	Intrinsic and extrinsic muscles of tongue	Movement of tongue	Hypoglossal nucleus


Spinal nerve fibers
Efferent (motor) fibers
Afferent (sensory) fibers
I
Olfactory
Nasal cavity
II
Optic
Eye
III
Oculomotor
Ciliary muscle, sphincter pupillae, and all external eye muscles except those below
IV
trochlear
Superior oblique muscle
VI
Abducent
Lateral rectus muscle
V
Trigeminal
Sensory-face, sinuses, Teeth, orbit and oral cavities, dura mater
Motor-muscles of mastication tensor tympani, tensor veli palatini, mylohyoid, anterior belly of disgastic
VII
Facial
Muscles of face, stapedius,posterior belly of disgastric, stylohyoid, occipitalis, auricularis muscles
Intermediate nerve
Motor-submandibular, sublingual, lacrimal glands Taste-anterior 2/3 of tongue, sensory soft palate
VIII
Vestibulocochlear
Cochlear
Vestibular
IX
Glossopharyngeal
Taste-posterior 1/3 of tongue
Sensory-tonsil, pharynx, middle ear
Motor-stylophyaryngeus, parotid gland
X
Vagus
Motor-heart, lungs, palate, pharynx, larynx, trachea, bronchi, GI tract
Sensory-heart, lungs, trachea, bronchi, larynx, pharynx, GI tract, external ear
XI
Accessory
Sternocleidomastoid, trapezius muscles
XII
Hypoglossal
Tongue muscles
Strap muscles (C1, 2, 3 fibers)

Cranial Nerves Pathway and Foramens

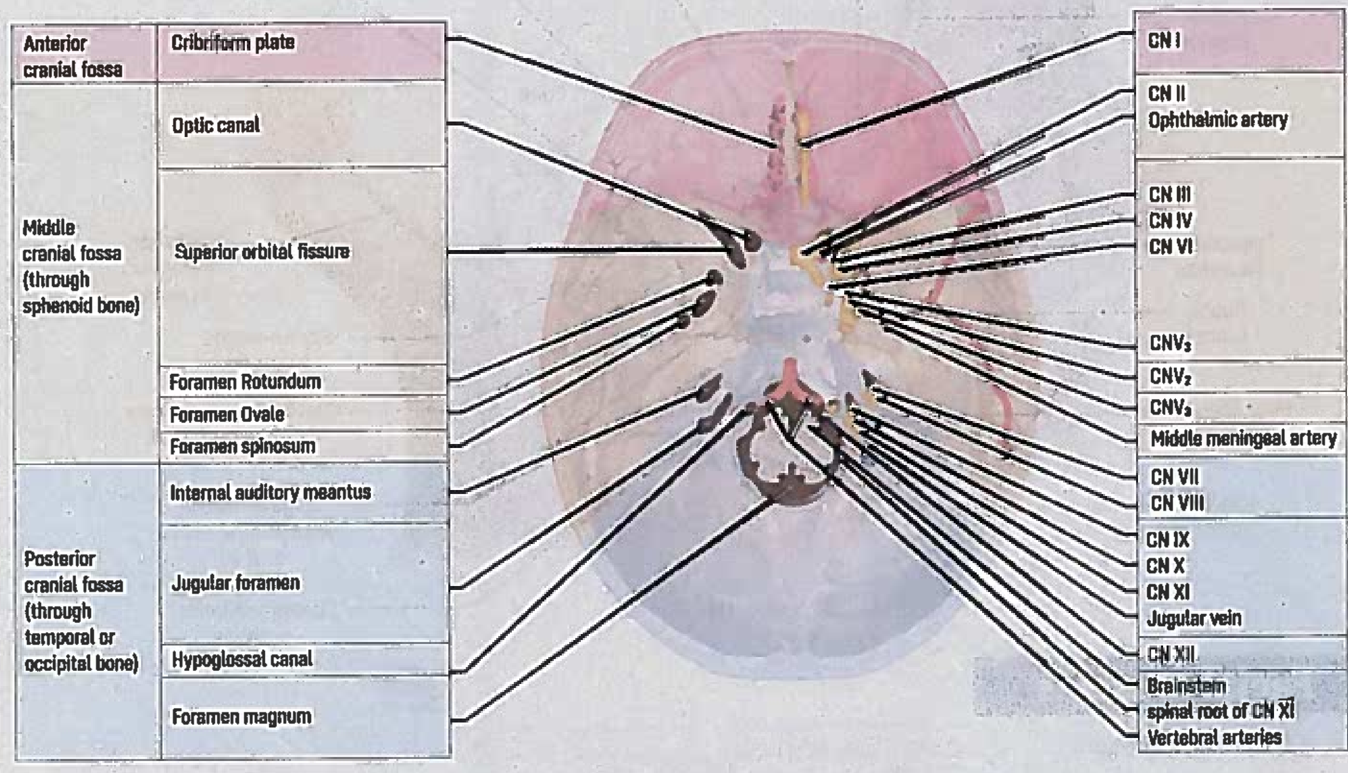
Anterior Cranial Fossa	• Cranial nerve I →Cribriform plate

Middle Cranial Fossa (CN II–VI)	• Contains cranial nerve from (CN II–VI)—through sphenoid bone
	• Optic Canal
	    • Cranial nerve II,, ophthalmic artery, central retinal vein
	• Superior orbital fissure
	    • Cranial nerve (CN III, IV, V1, VI), ophthalmic vein
	• Foramen Rotundum
	    • V2
	• Foramen Ovale
	    • V3
	• Foramen Spinosum
	    • Middle meningeal artery
	MNEMONIC: Cranial nerve V → Standing Room Only

Posterior Cranial Fossa (CN VII–XII)	• Contains CN VII–XII—through temporal or occipital bone
	    • Internal auditory meatus →Cranial nerve (CN VII, VIII)
	    • Jugular foramen →Cranial nerve(CN IX, X, XI, jugular vein)
	    • Hypoglossal canal →CN XII

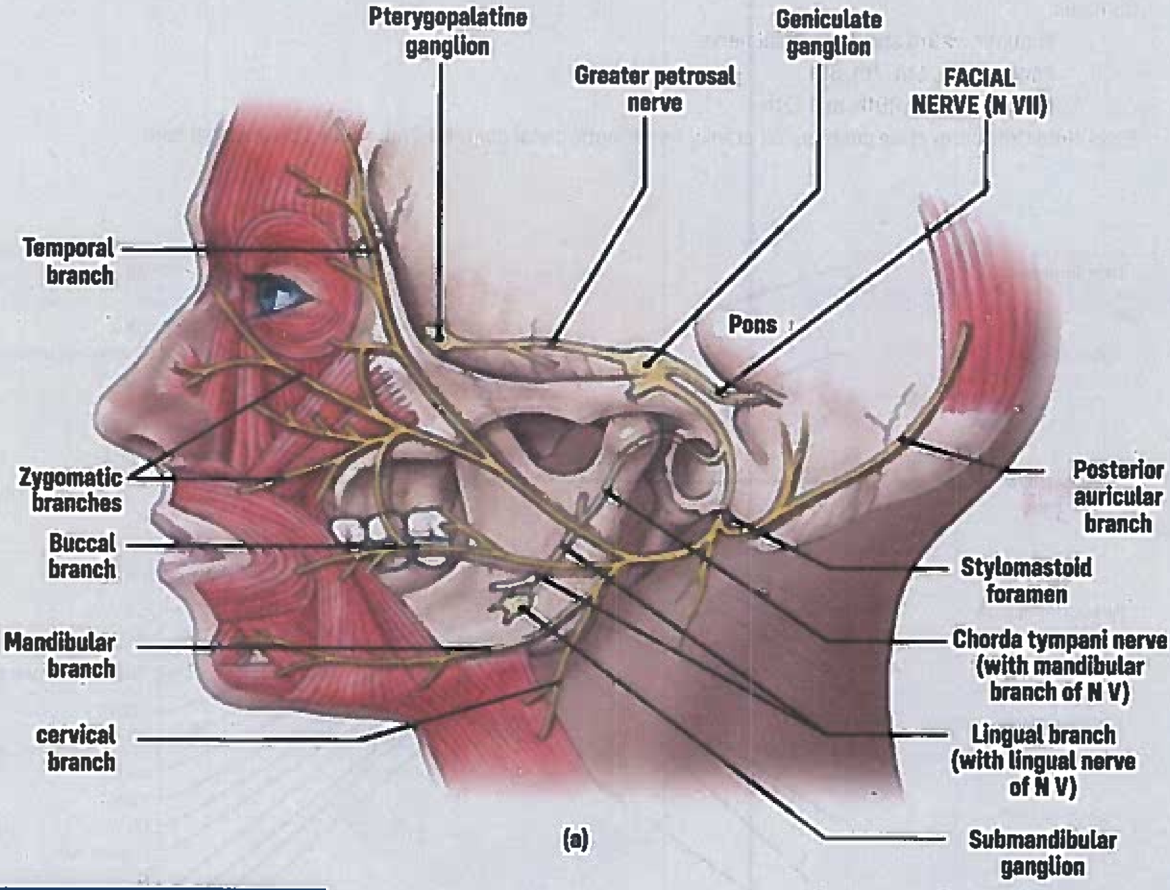
Location of Cranial Nerve Nuclei in Brain Stem

- Contains
  - Midbrain →3rd and 4th cranial nerve
  - Pons →5th, 6th, 7th, 8th
  - Medulla →9th, 10th, and 12th
- Extra Note Cribriform plate contains 1st cranial nerve, optic canal contains 2nd, while 11th in spinal cord



Facial Nerve

- 7th cranial nerve, nerve of 2nd branchial arch
- Leaves skull by passing through stylomastoid foramen
- In its extra cranial course:
  - Crosses lateral side of styloid process
  - Enters parotid gland
  - Behind neck of mandible divides into five terminal branches
- Branches and distribution:
  - **Within Facial Canal:**
    - Greater petrosal nerve
    - Nerve to Stapedius
    - Chorda tympani
  - **At Its Exit From Stylomastoid Foramen:**
    - Posterior auricular
    - Posterior belly of Digastric muscle
    - Stylohyoid
  - **Terminal Branches Within Parotid Gland** (Two Zombies Buggered My Cat)
    - Temporal
    - Zygomatic
    - Buccal
    - Mandibular
    - Cervical

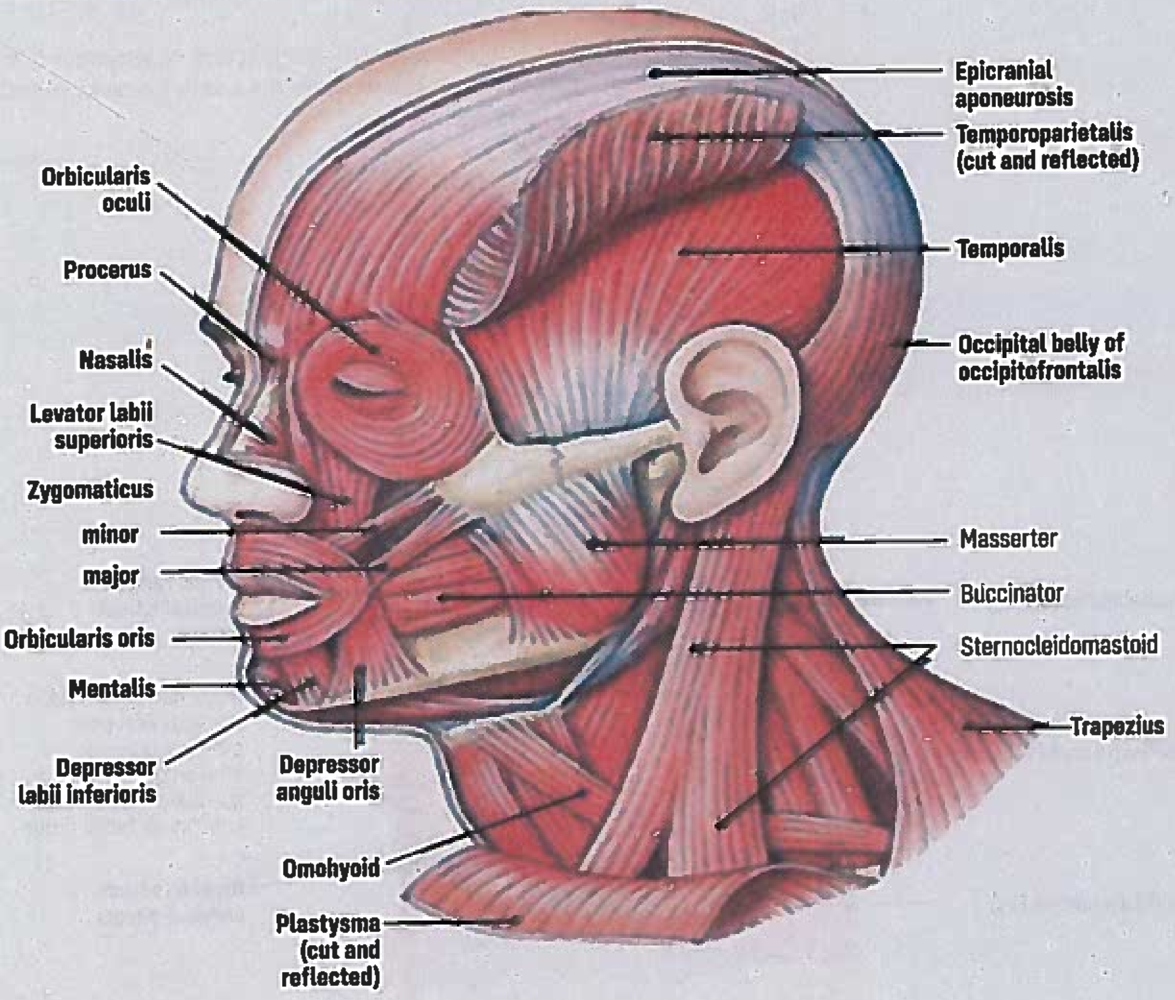


(a)

Facial Muscles

Blood Supply Of Face	• Facial artery • Transverse facial artery

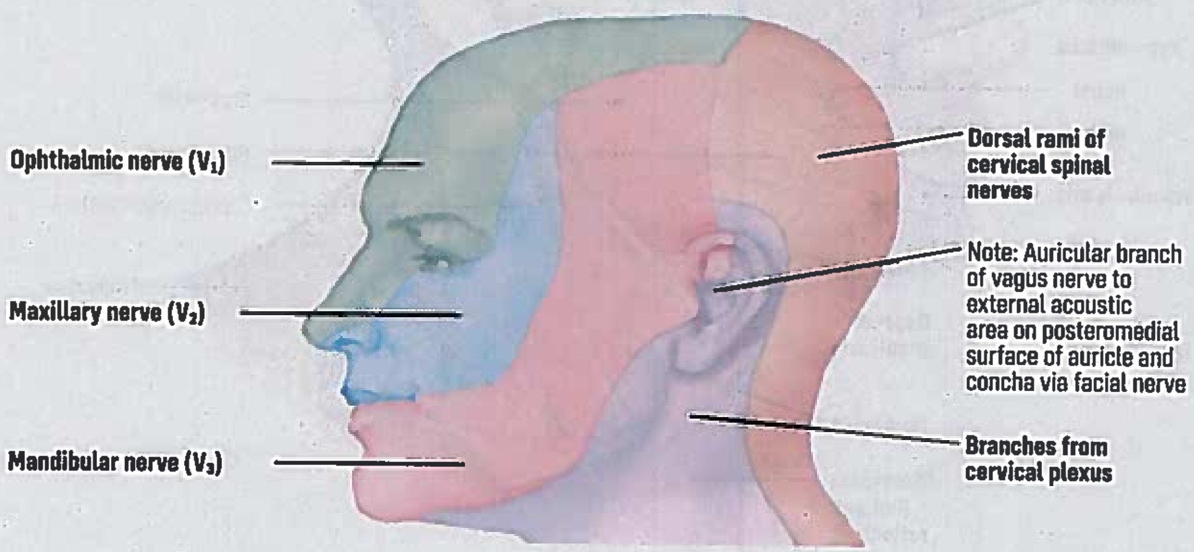
Nerve Supply	• **Motor nerve supply** · Facial nerve • **Sensory nerve supply** · Trigeminal nerve · Greater auricular nerve→ supplies skin over angle of jaw and over parotid gland	
Common Facial Expression	**Facial Expressions**	**Muscles**
	Smiling And Laughing	• Zygomaticus major
	Sadness	• Levator labi superioris • Levator anguli Oris
	Grief	• Depressor anguli Oris
	Anger	• Dilator naris • Depressor septii
	Frowning	• Corrugator supercilli • Procerus
	Horror, Terror And Fright	• Platysma
	Surprise	• Frontalis
	Doubt	• Mentalis
	Grinning	• Risorius
	Contempt	• Zygomaticus major



Sensory Nerve Supply of Face and Mouth

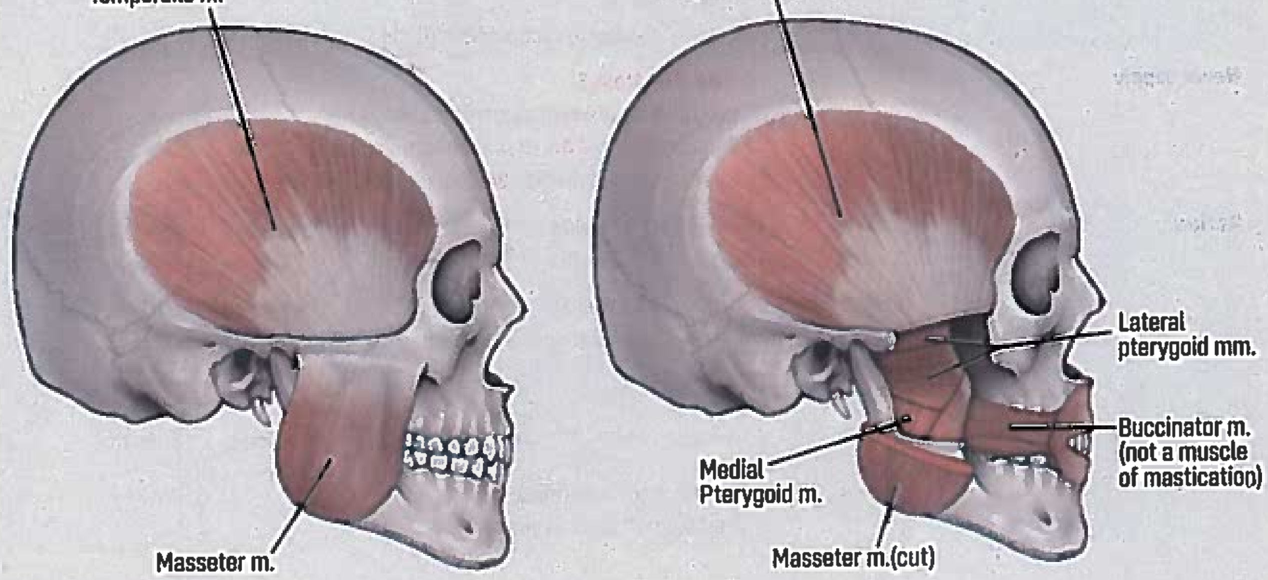
Greater Auricular Nerve (C2-C3)	• Supplies skin over angle of jaw and over parotid gland

Trigeminal Nerve	• The largest cranial nerve
	• Three (tri) major branches
	• **Ophthalmic nerve (V1)**
	  ◦ Sensory
	  ◦ Carries sensory information from the scalp, forehead, the upper eyelid, the conjunctiva and cornea of the eye, the nose (including the tip of the nose, except alae nasi), the Frontal sinuses and parts of the meninges (the dura and blood vessels).
	• **Maxillary nerve (V2)**
	  ◦ Sensory
	  ◦ Carries sensory information from the lower eyelid and cheek, the nares and upper lip, the upper teeth and gums, the nasal mucosa, the palate and roof of the pharynx, the Maxillary, Ethmoid and Sphenoid sinuses and parts of the meninges
	• **Mandibular nerve (V3).**
	  ◦ Sensory and motor
	  ◦ Carries sensory information from the lower lip, the lower teeth and gums, the chin and jaw (except the angle of the jaw, which is supplied by Greater auricular nerve), parts of the external ear and parts of the meninges
	  ◦ Motor part supplies muscle of mastication, anterior belly of digastric and mylohoid muscles
	• Note
	The Mandibular nerve carries touch-position and pain-temperature sensations from the mouth. Although it does not carry taste sensation (the chorda tympani which is a branch of facial nerve is responsible for taste)
	
	V1 passes thru → Superior orbital fissure
	V2 passes thru → Foramen Rotundum
	V3 passes thru → Foramen Ovale
	MNEMONIC: Cranial nerve V → Standing Room Only



Muscles of Mastication

- Develop from mesoderm of 1st brachial arch.
- All supplied by mandibular division of trigeminal nerve
  - **M**asseter (closes the mouth)
  - Te**M**poralis (closes the mouth)
  - **M**edial pterygoid (closes the mouth)
  - **L**ateral pterygoid (opens the mouth)
- Mnemonic:
  - while you say **L**– your mouth opens – Lateral pterygoid opens mouth
  - while you say **M**—your mouth closes—so opens **M**outh



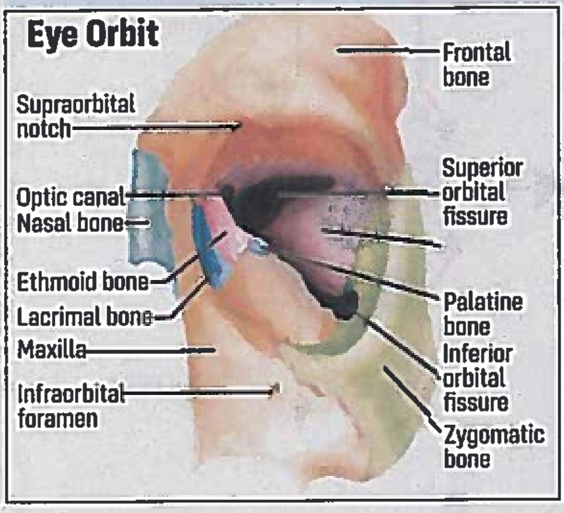
ORBIT

Orbital Margin

Formed by frontal, maxilla and zygomatic bone

Contents Of Orbit

- Eyeball
- Fascia
- Muscles:
  - Extraocular
- Vessels:
  - Ophthalmic artery
  - Superior and inferior ophthalmic veins
  - Lymphatics
- Nerves:
  - Optic
  - Occulomotor
  - Trochlear
  - Abducent branches of ophthalmic nerve
  - Maxillary nerve
  - Sympathetic nerve
- Lacrimal gland
- Orbital fat



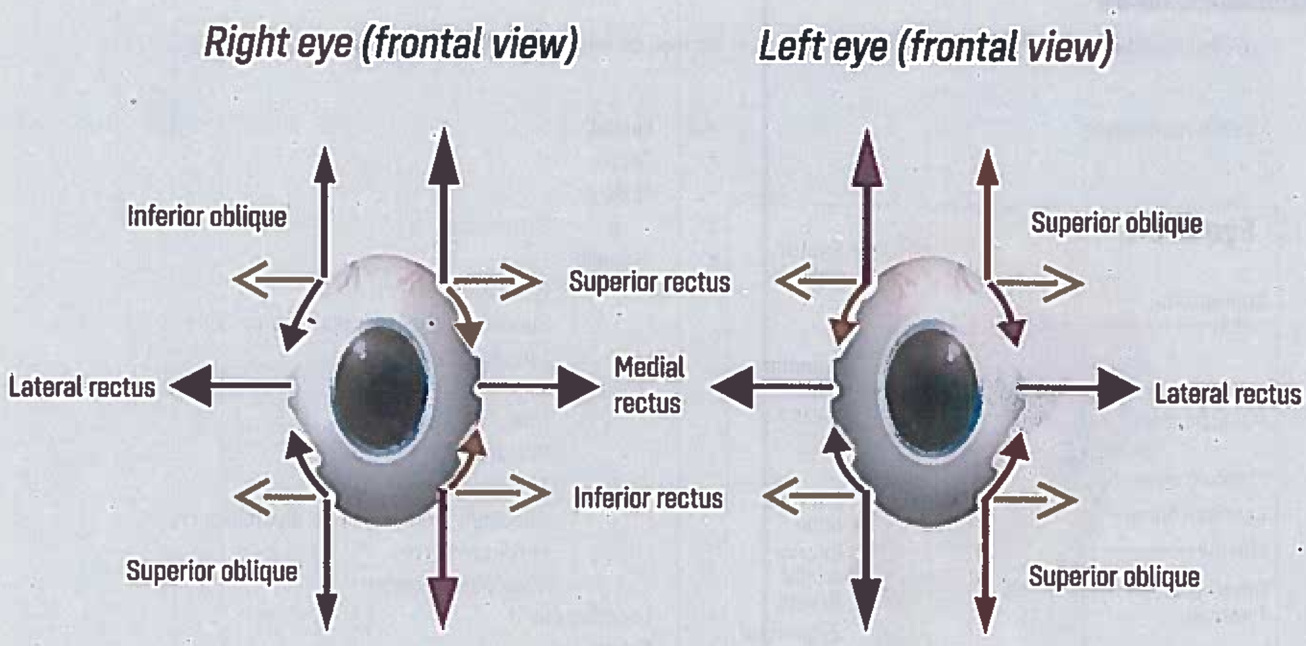
Muscles	• Extraocular: (voluntary)
	  • 4 Recti: (arises from a common origin—common annular tendon)
	    • Superior rectus
	    • Inferior rectus
	    • Medial rectus
	    • Lateral rectus
	• 2 oblique:
	  • Superior oblique
	  • Inferior oblique
	• Intraocular muscles: (involuntary)
	  • Ciliary muscle
	  • Constrictor and dilator pupillae of iris

Nerve supply	• Mnemonic: **LR6-SO4 Rest 3**
	  • **L**ateral **R**ectus **6th** (abducent) cranial nerve
	  • **S**uperior **O**blique **4th** (trochlear) cranial nerve
	  • **Rest** all are supplied by **3rd** (occulomotor) nerve

Action

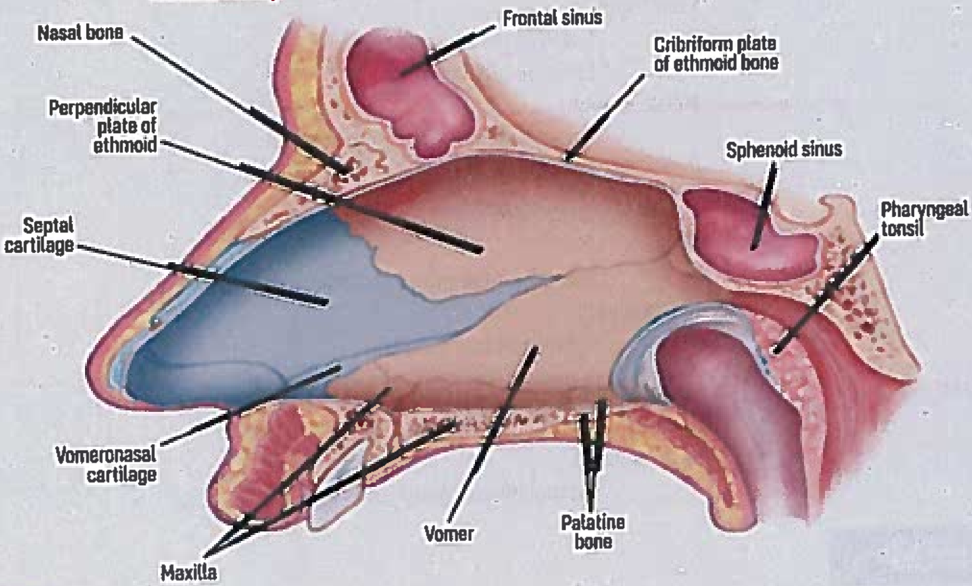
Superior Rectus	Inferior Rectus	Medial Rectus	Lateral Rectus	Superior Oblique	Inferior Oblique
Upward rotation Medial rotation Intortion	Downward rotation Medial rotation Extortion	Medial rotation	Lateral rotation	Downward rotation Lateral rotation Intortion	Upward rotation Lateral rotation Extortion

• Levator palpebrae superioris (muscle of eyelid):
  • Elevation of upper eyelid



Nose

- Divided into external nose and nasal septum
- External nose → Formed by nasal bones, frontal process of maxilla and cartilages.
- Nasal septum:
  - Partition b/w two halves of nose
  - Extends from nostril in front to choanca behind
  - Bony part →Vomer, Perpendicular part of Ethmoid bone
  - Cartilaginous part → Septal cartilage
- Blood supply:
  - Maxillary artery supplies nasal cavity
  - The sphenopalatine branch anastomoses with septal branch of facial artery (a common site for nasal bleeds).



Tongue

- A middle fibrous septum divides the tongue into right and left halves
- Each half contains four intrinsic and four extrinsic muscles.

Muscles	Intrinsic muscles	Extrinsic muscles
	• Superior longitudinal • Inferior longitudinal • Transverse • Vertical	• Genioglossus • Hyoglossus • Styloglossus • Palatoglossus
Arterial Supply	• Lingual artery	

Nerve Supply	• Motor nerves:
	  ◦ All except palatoglossus muscle: hypoglossal nerve
	  ◦ Palatoglossus muscle: accessory nerve through pharyngeal plexus.
	• Sensory nerves:
	  ◦ **Ant 2/3rd: (formed from 1st and 2nd branchial arches)**
	    ▪ General sensation: lingual nerve (mandibular branch)
	    ▪ Taste sensation: chorda tympani (facial nerve)
	  ◦ **Post 1/3rd: (formed from 3rd and 4th branchial arches)**
	    ▪ General and taste sensation: glossopharyngeal nerve	

Salivary Glands

- 3 in number→ parotid, submandibular and sublingual

Parotid Gland	• Largest of salivary gland
	• Structures within parotid gland:
	  ◦ Arteries:
	    ▪ External carotid artery
	    ▪ Maxillary artery
	    ▪ Superficial temporal vessels
	    ▪ Posterior auricular artery
	  ◦ Veins:
	    ▪ Retromandibular vein
	  ◦ Nerves:
	    ▪ Facial nerve
	• Parotid duct:
	  ◦ Opens into mouth opposite crown of upper 2_{nd} molar tooth.
	• Blood supply:
	  ◦ External carotid artery
	  ◦ External jugular vein
	• Nerve supply:
	  ◦ Parasympathetic and sympathetic.
	  ◦ Sensory→ from Auriculotemporal nerve

Submandibular Gland	• Lies in digastric triangle
	• Duct:
	  ◦ Opens on floor of mouth at sides of frenulum
	• Nerve supply:
	  ◦ Submandibular ganglion

Sublingual Gland	• Smallest of all • 15 ducts arises from it and opens on floor of mouth • Nerve supply: ◦ Submandibular ganglion

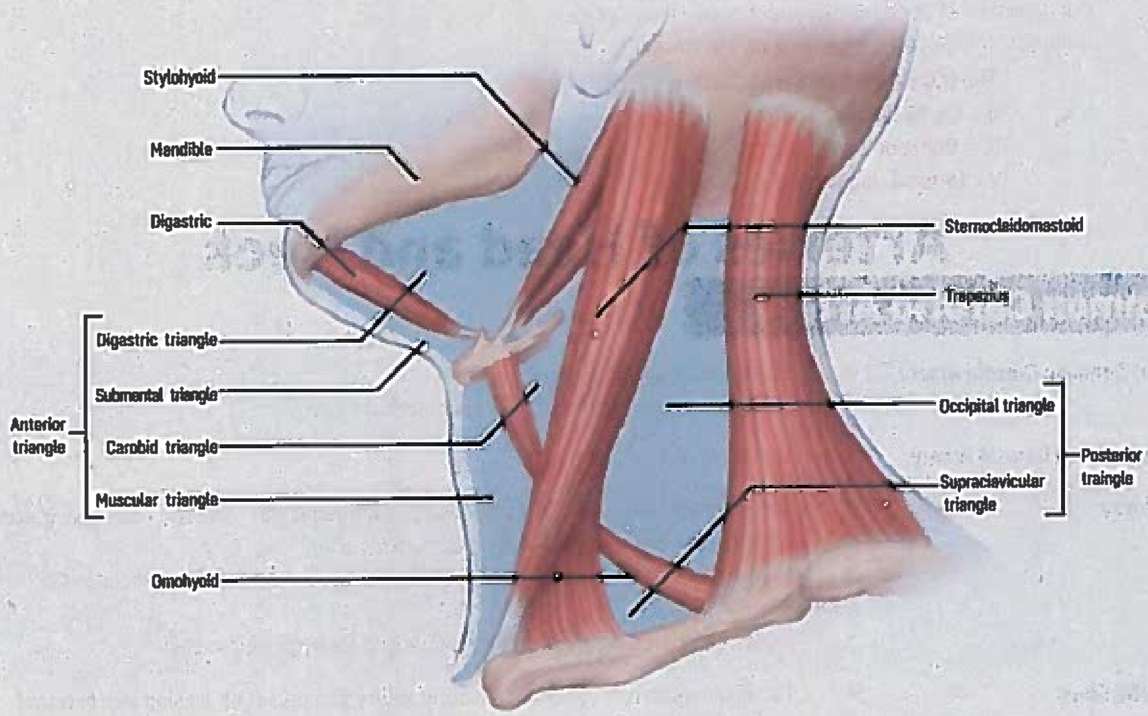
Vagal Nuclei

Nuclei	Function	Cranial Nerves
Nucleus Solitarius	Sensory information (e.g., taste, baroreceptors, gut distention)	VII, IX, X
Nucleus aMbiguus	Motor innervation of pharynx, larynx, upper esophagus (e.g., swallowing, palate elevation)	IX, X, XI (cranial portion)
DorsAl motor nucleus	Autonomic (parasympathetic) fibers to heart, lungs, upper GI	X

Triangles of Neck

Anterior Triangle	Posterior Triangle

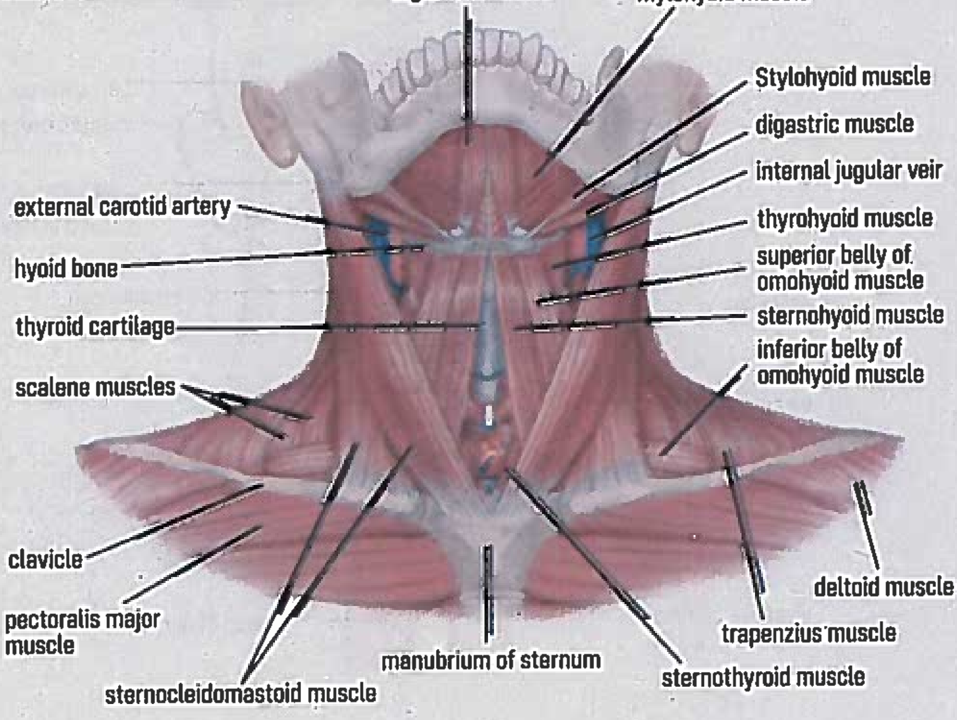
• Boundaries:
  ◦ Anteriorly: middle line of neck
  ◦ Posteriorly: anterior border of sternocleidomastoid muscle
  ◦ Superiorly: lower border of mandible
• Further subdivisions:
  ◦ Carotid triangle
  ◦ Submental triangle
  ◦ Digastric (submandibular triangle)
  ◦ Muscular triangle
	• Boundaries:
	  ◦ Anteriorly: posterior border of sternocleidomastoid
	  ◦ Posteriorly: anterior border of trapezius
	  ◦ Inferiorly: middle $1/3_{rd}$ of clavicle
	• Contents:
	  ◦ Subclavian artery (3rd part) and subclavian vein
	  ◦ External jugular vein
	  ◦ Brachial plexus
	  ◦ Branches of cervical plexus
	  ◦ Spinal part of accessory nerve



Muscles of Neck

Infrahyoid Muscles	Suprahyoid Muscles
mnemonic: TOSS My Gravy Spoon, Darling	
Muscles below the hyoid bone	Muscles above the hyoid bone
• Thyrohyoid	• Mylohyoid
• Omohyoid	• Geniohyoid
• Sternohyoid	• Stylohyoid
• Sternothyroid	• Digastric

Muscles of the neck



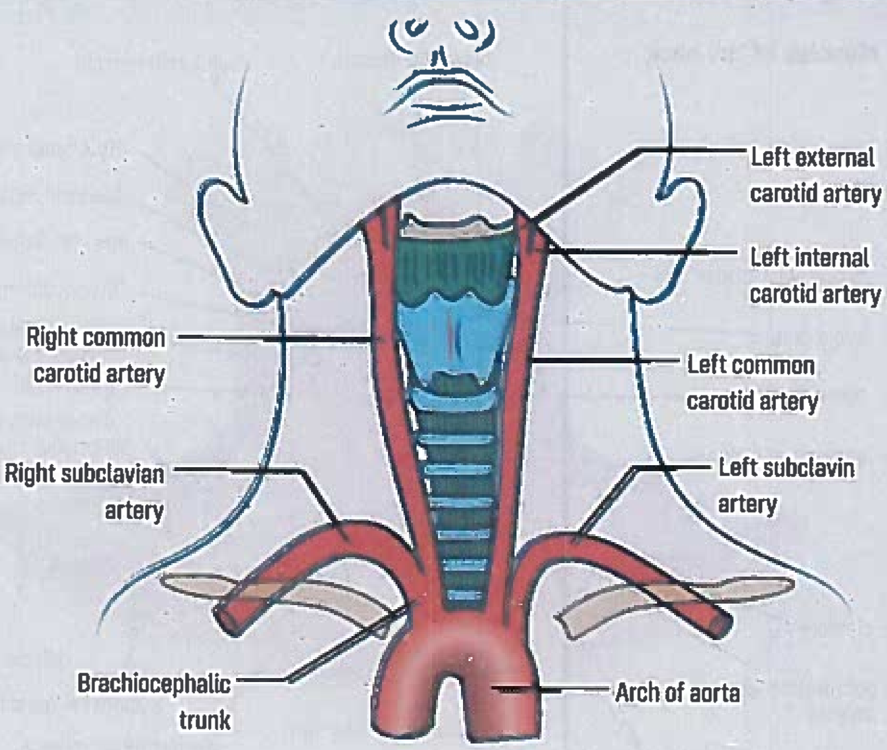
Carotid Sheath

- Condensation of deep fascia around main vessels of neck
- Contents: (mnemonic → I See 10 CC's in the IV)
  - I See (I.C.) = Internal Carotid artery
  - 10 = CN 10 (Vagus nerve)
  - CC = Common Carotid artery
  - IV = Internal Jugular Vein

Arteries of Head and Neck

Common Carotid Artery

Right Common Carotid Artery	• Branch of brachiocephalic artery • It begins in neck behind right sternoclavicular joint
Left Common Carotid Artery	• Branch of arch of aorta
Pathway	• The common carotid artery runs upward in carotid sheath through neck undercover on anterior border of sternocleidomastoid muscle • At upper border of thyroid cartilage it divides into external and internal carotid arteries • In carotid sheath artery is related laterally to internal jugular vein
Carotid Sinus	• Localized dilatation of common carotid artery at its point of division into external and internal carotid artery • Act as a baroreceptor and regulates blood pressure • Nerve supply: glossopharyngeal nerve.
Carotid Body	• Small structure that lies posterior to point of division of common carotid artery • Chemoreceptor: responds to changes in oxygen and CO2, assists in regulating heart and respiratory rates • Nerve supply: glossopharyngeal nerve
Branches	• External and internal carotid artery



External Carotid Artery

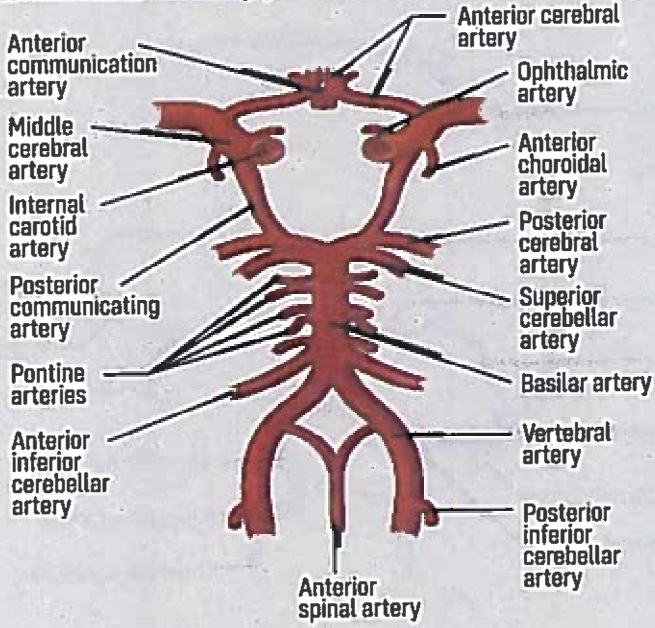
- Begins at level of upper border of thyroid cartilage, lies anterior to internal carotid artery
- Emerges from undercover of anterior border of sternocleidomastoid muscle lies within carotid triangle
- Terminates in parotid salivary glands, divides into superficial temporal and maxillary artery.
- Branches: (Mnemonic-- Some Anatomists Like Freaking Out Poor Medical Students)
  - 8 branches:
    - Superior thyroid
    - Ascending pharyngeal
    - Lingual
    - Facial
    - Occipital
    - Posterior auricular
    - Maxillary
    - Superficial temporal.

Internal Carotid Artery

- Begins at upper border of thyroid cartilage
- Ascends in neck in carotid sheath
- Passes deep to parotid gland
- Enters cranial cavity by passing through carotid canal in petrous part of temporal bone.
- Upward and forward in cavernous sinus
- Divides into anterior and middle cerebral arteries
- Branches:
  - Corticotympanic branches
  - Ophthalmic artery
  - Posterior Communicating artery
  - Anterior cerebral artery
  - Middle cerebral artery

Circle of Willis

- Lies in subarachnoid space of brain
- Formed by anastomosis between two internal carotid arteries and two vertebral arteries
- Anterior communication:
  - Internal carotid and anterior cerebral artery (both are branches of ICA)
- Posterior communication:
  - Posterior cerebral and basilar artery. (both are the branches of vertebral arteries)



Cavernous Sinus

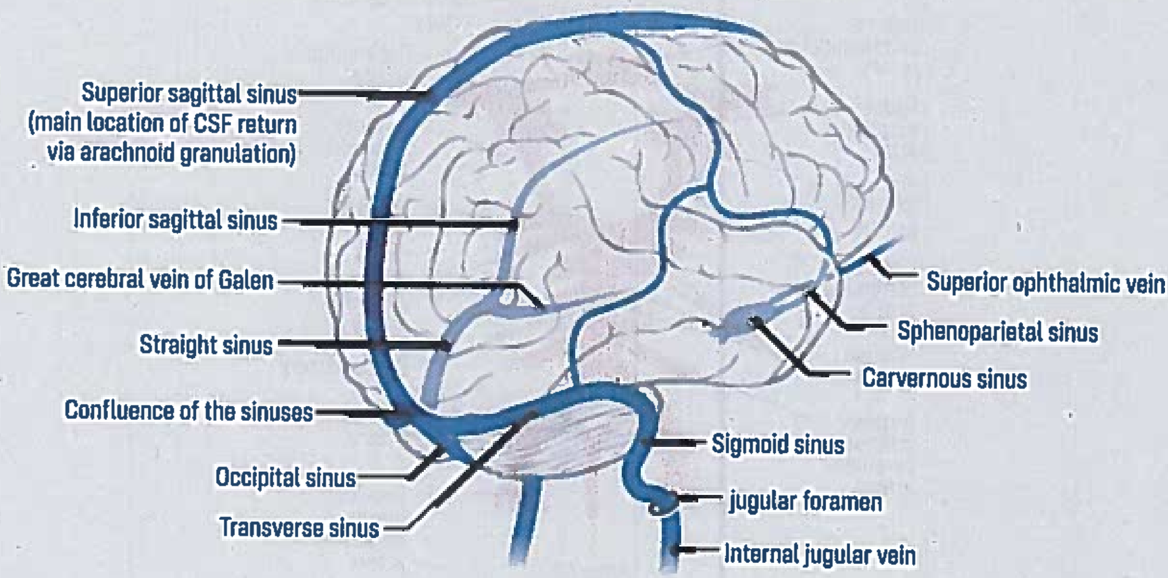
Location and Drainage	• The cavernous sinus is located on either side of the pituitary fossa and body of the sphenoid bone → drains into internal jugular vein.
Contains	• CN 3rd, 4th, 5th (V1, V2) and 6th cranial nerve • Internal carotid artery • Facial vein and inferior ophthalmic vein (note these are an important route for spread of infection from face) • 6th cranial nerve is most susceptible to injury
Cavernous Sinus Syndrome	• Presents with variable ophthalmoplegia, ↓ corneal sensation, Horner syndrome and occasional decreased maxillary sensation. 2° to pituitary tumor mass effect, carotid-ca ernous fistula, or cavernous sinus thrombosis related to infection.
Caveronus Sinus Vs Lateral Sinus Thrombosis	**Cavernous Sinus Thrombosis** • Periorbital oedema • Ophthalmoplegia: **6th nerve damage** typically occurs before 3rd & 4th • Trigeminal nerve involvement may lead to hyperaesthesia of **upper face and eye pain** • central retinal vein thrombosis **Lateral Sinus Thrombosis** • **6th and 7th cranial nerve palsies**

Dural Venous Sinuses

- Large venous channels that runs through the dura. Drain blood from cerebral veins (arrow) and receive CSF from arachnoid granulations. Empty into internal jugular vein
  - Superior sagittal sinus lies in upper portion of Falx cerebri →drain into right transverse sinus
  - Inferior sagittal sinus + great cerebral vein of gallen →drains into straight sinus → which then drains into left transverse sinus
  - Right and left transverse sinus drains into → sigmoid sinus→ internal jugular vein

Venous Sinus Thrombosis

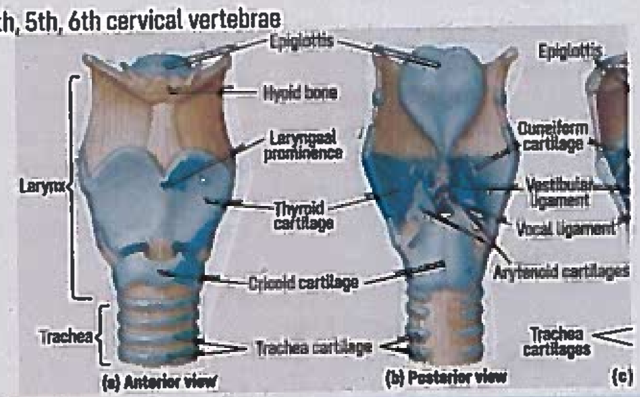
- Presents with signs/symptoms of ↑ ICP (e.g., headache, seizures, and focal neurologic deficits).
- May lead to venous hemorrhage.
- Associated with hypercoagulable states (e.g. Pregnancy, OCP use, factor V Leiden).



Organs in Head and Neck

Larynx

- Organ for production of voice
- Lies in anterior midline of neck, in front of 3rd, 4th, 5th, 6th cervical vertebrae
- Cartilages of larynx:
  - 9 cartilages. 3 paired, 3 unpaired
  - Unpaired cartilages:
    - Thyroid
    - Cricoid
    - Epiglottic
  - Paired cartilages:
    - Arytenoids
    - Corniculate
    - Cuneiform



Thyroid	• V- Shaped, Largest cartilage of larynx and consists of two laminae. • Each of which has a superior and inferior cornu • Inferior cornu articulates with the cricoid cartilage to form cricothyroid joint
Cricoid	• Ring shaped. • Narrow anterior part called arch, and broad posterior part called lamina. • The lamina articulates superiorly with arytenoid cartilages
Epiglottic	• Leaf shaped, lies behind root of tongue and attach by its stalk to thyroid cartilage
Arytenoids	• 2 arytenoid cartilages, pyramidal in shape • Articulate with cricoid
Corniculate	• Articulate with arytenoid cartilages
Cuneiform	• Strengthen aryepiglotic folds

Action of Laryngeal Muscles

Muscles which open glottis	Muscles which close glottis	Muscles which tense the vocal cords	Muscles which relax the vocal cords	Muscles which open the inlet of larynx
Posterior cricoarytenoid	Lateral cricoarytenoids Transverse arytenoids Cricothyroid Thyroarytenoid	Cricothyroid	Thyroarytenoids	Thyroepiglotticus

Arterial Supply

- Upto vocal cords: superior laryngeal artery (branch of superior thyroid artery)
- Below vocal cords: inferior laryngeal artery (branch of inferior thyroid artery)

Nerve supply

- Motor nerve: (mnemonic—**SCAR**----larny**X** is supplied by **X** cranial nerve(vagus via nucleus ambiguus, laryngeal nerves are branches of vagus nerve)
  - **S**uperior laryngeal nerve →**C**ricothyroid:
  - **A**ll other muscles (except cricothyroid) →**R**ecurrent laryngeal nerve
- Sensory nerve:
  - Above vocal cords: internal laryngeal nerve (branch of superior laryngeal nerve)
  - Below vocal cords: recurrent laryngeal nerve

Glands in Head and Neck

Pituitary Gland: (Hypophysis Cerebri)

- Located in hypophyseal fossa in sella Tercica of sphenoid bone.
- Divided into anterior lobe (adenohypophysis) and a posterior lobe (neurohypophysis).
- **Important relations:**
  - Anteriorly: sphenoid sinus
  - Posteriorly: dorsam sellae, basilar artery and pons
  - Superiorly: dipaphragma sellae and optic chiasma
  - Inferiorly: body of sphenoid
  - Laterally: cavernous sinus and its contents (internal carotid artery, abducent nerve)
- **Blood supply:**
  - Superior and inferior hypophyseal arteries
  - Internal carotid artery
- **Clinical anatomy:**
  - Enlargement of pituitary due to tumor or other can result in pressure on optic chiasma resulting in bitemporal hemianopia

Thyroid Gland

- Consists of right and left lobe connected by isthmus
- Surrounded by sheath formed of pretracheal fascia
- This sheath attaches the gland to larynx and trachea.
- Each lobe of gland is pear shaped.
- Isthmus crosses the midline in front of 2nd, 3rd, and 4th rings of trachea
- The gland lies against vertebrae C5,C6,C7 and T1
- Larger in females as compared to males and further increases in size during menstruation and pregnancy.
- **Embryology:**
  - Thyroid gland is derived from: endoderm.
  - Thymus and inferior parathyroid develops from: 3rd branchial pouch.
  - Superior para thyroid is developed from: 4th brachial pouch.
- **Arterial supply:**
  - Superior thyroid artery (related to external laryngeal nerve)
  - Inferior thyroid artery (related to recurrent laryngeal nerve)
  - Thyroida ima artery (3%individuals) from brachiocephalic artery
- **Venous drainage:**
  - Thyroid gland lymph drainage = deep cervical lymph nodes
  - Inferior thyroid veins drains into= brachiocephalic vein
  - Superior and middle thyroid vein drains into= internal jugular vein
- **Clinical anatomy**
  - Most common nerve injured overall → external laryngeal nerve
  - During Thyroidectomy nerve damaged → external laryngeal nerve
  - During Tracheostomy nerve damaged → recurrent laryngeal nerve
  - Internal laryngeal nerve passes through= thyroid and hyoid

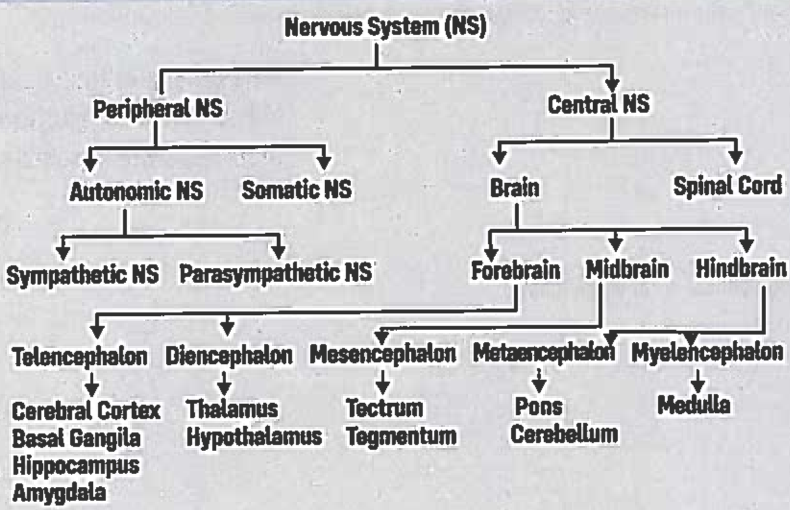
Chapter 2: Neurology

Classification of Nervous System

- Nervous system is divided into central and peripheral nervous system

Central Nervous System	• Central nervous system (CNS) includes brain and spinal cord. • Brain is situated in the skull. It is continued as spinal cord in the vertebral canal through the foramen magnum of the skull bone. • Brain and spinal cord are surrounded by three layers of meninges called the outer dura mater, middle arachnoid mater and inner pia mater. • The space between arachnoid mater and pia mater is known as subarachnoid space. • This space is filled with a fluid called cerebrospinal fluid.

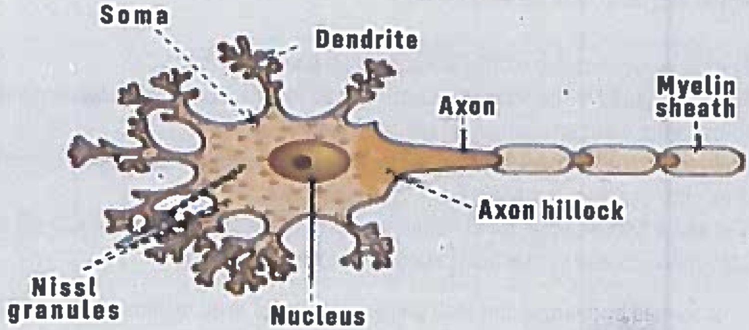
Peripheral Nervous System	• Is formed by neurons and their processes present in all regions of the body. It consists of cranial nerves arising from brain and spinal nerves arising from the spinal cord.
	• It is again divided into two subdivisions
	  • <u>**Somatic nervous system:**</u>
	    • Somatic nervous system is concerned with somatic functions.
	    • It includes the nerves supplying the skeletal muscles.
	    • Somatic nervous system is responsible for muscular activities and movements of the body.
	  • <u>**Autonomic nervous system:**</u>
	    • Autonomic nervous system is concerned with regulation of visceral or vegetative functions. So, it is other wise called vegetative or involuntary nervous system.
	    • Autonomic nervous system consists of three divisions,
	      • Sympathetic division (thoraco-lumbar outflow T1-L3)
	      • Parasympathetic division (cranio-sacral outflow III VII IX and X, S2-S4).
	      • Enteric division: relays information from sympathetic and parasympathetic nervous system to GI tract



Neuron

- Neuron or nerve cell is defined as the structural and functional unit of nervous system.
- Neuron is similar to any other cell in the body, having nucleus and all the organelles in cytoplasm.
- However, it is different from other cells by two ways:
  - Neuron has branches or processes called axon and dendrites
  - Neuron does not have centrosome. So, it cannot undergo division.
- Neuron is made up of three parts:
  - Soma or cell body or perikaryon: it contains cytoplasm containing a large nucleus, Nissl bodies, neurofibrils, mitochondria and Golgi apparatus. Nissl bodies and neurofibrils are found only in nerve cell and not in other cells.
  - Dendrites: carry impulses towards cell body
  - Axon: carry impulses away from cell body

Axon hillock:
•Region of ell body where axon originates
•Nissl granules/body are absent here



Grey matter and white matter

- Grey matter: it is composed of nerve cell bodies embedded in neuroglia.
- White matter: it is composed of nerve fibers embedded in neuroglia while appearance is due to myelin sheath.
- Distribution:
  - In cerebrum and cerebellum →grey matter is outside and white matter is inside.
  - In spinal cord →grey matter is inside and white matter is outside.

Neuroglia (Nerve Glue)

- These are non-excitable connective tissue cells forming interstitial supporting tissue of CNS, present in both grey and white matter.
- Neuroglia of CNS:
  - Astrocytes → Derived from neuroectoderm
  - Oligodendroglia (make CNS myelin)
  - Microglia
- Neuroglia of PNS:
  - Schwann cells.(make myelin for PNS, Derived from neural crest.-----injured in GBS)

Dale principle: each neuron releases only one kind of neurotransmitter at all of its separate terminals.

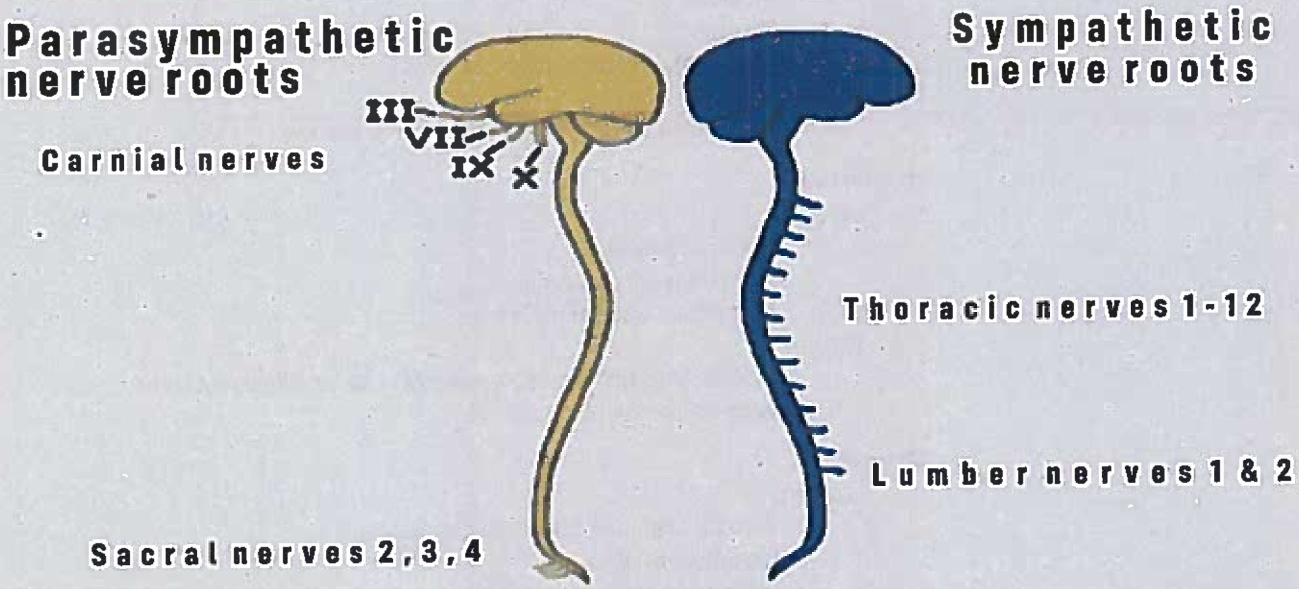
Ganglion

- Collection of cell bodies is called ganglion

Autonomic Nervous System

Organization of ANS

Preganglionic Neurons	• Sympathetic nervous system originate in spinal cord segments T1–L3 or the thoracolumbar region. • Parasympathetic nervous system originate in the nuclei of cranial nerves (3, 7, 9, and 10) and in spinal cord segments S2–S4 or the craniosacral region.
Postganglionic Neurons	• Both Sympathetic and Parasympathetic nervous system have their cell bodies in the autonomic ganglia and synapse on effector organs (e.g., heart, blood vessels, and sweat glands).



Neurotransmitters of ANS

Adrenergic Neurons	Release Norepinephrine as the neurotransmitter
Cholinergic Neurons	Release Acetylcholine (ACh) as the neurotransmitter

Sympathetic and Parasympathetic Fibers

Sympathetic Fibers	Parasympathetic Fibers
Preganglionic Fibers →Acetylcholine (Ach)	Preganglionic Fibers →ACh
Postganglionic Cholinergic Fibers→ ACh (e.g. sweat	Postganglionic Fibers →ACh
Postganglionic Noradrenergic Fibers →Noradrenaline	

Myelin

- ↑conduction velocity of signals transmitted down axons
- Saltatory conduction of action potential at the nodes of Ranvier, where there are high concentrations of Na+ channels.
- Synthesis of myelin by oligodendrocytes in CNS
- Synthesis of myelin by Schwann cells in PNS

Receptor Types in ANS

Adrenergic receptors (adrenoreceptors)	**α1 receptors**
	• Location:
	  ◦ Vascular smooth muscle of the skin
	  ◦ Splanchnic regions
	  ◦ The gastrointestinal (GI) and bladder sphincters
	  ◦ Radial muscle of the iris.
	• Action
	  ◦ Produce excitation (e.g., contraction or constriction)
	
	α2 receptors
	• Location:
	  ◦ Platelets
	  ◦ Fat cells
	  ◦ Walls of the GI tract (heteroreceptors).
	• Action
	  ◦ Often produce inhibition (e.g., relaxation or dilation)
	
	β1 receptors
	• Location:
	  ◦ Sinoatrial (SA) node
	  ◦ Atrioventricular (AV) node
	  ◦ Ventricular muscle of the heart.
	• Action
	  ◦ Produce excitation (e.g., increased heart rate, increased conduction velocity, increased contractility).
	
	β2 receptors:
	• Location:
	  ◦ Vascular smooth muscle of skeletal muscle
	  ◦ Bronchial smooth muscle
	  ◦ Walls of the GI tract and bladder.
	• Action
	  ◦ Produce relaxation (e.g., dilation of vascular smooth muscle, dilation of bronchioles, relaxation of the bladder wall)

Cholinergic Receptors (Cholinoreceptors)	**Nicotinic Receptors**
	• Location:
	  ◦ Autonomic ganglia (NN) of the sympathetic and parasympathetic nervous systems, at the neuromuscular junction (NM), and in the adrenal medulla (NN).
	• Activation
	  ◦ ACh or nicotine.
	• Action
	  ◦ Produce excitation.
	
	Muscarinic Receptors
	• Location:
	  ◦ Heart (M2)
	  ◦ Smooth muscle (M3), and
	  ◦ Glands (M3).
	• Activation
	  ◦ ACh and muscarine
	• Action
	  ◦ Inhibition in heart (e.g., decreased heart rate, decreased conduction velocity in AV node).
	  ◦ Excitatory in smooth muscle and glands (e.g., increased GI motility, increased secretion).
	  ◦ Are blocked by atropine

Effect of the Autonomic Nervous System on Organ Systems

- Remember a rule, α1 is for constriction, α2 is for inhibition, β1 is for heart, β2 is for relaxation

Organ	Sympathetic Action	Receptor	Parasympathetic Action	Parasympathetic Receptor
Heart	↑ heart rate	β1	↓ heart rate	M2
	↑ contractility	β1	↓ contractility	M2
	↑ AV node conduction	β1	↓ AV node conduction	M2
Vascular smooth muscle	Constricts blood vessels in skin; splanchnic	α1	-------------	
	Dilates blood vessels in skeletal muscle	β2	-------------	
Gastrointestinal tract		α2, β2		M3
	Constricts sphincters	α1	Relaxes sphincters	M3
Bronchioles	Dilates bronchiolar smooth muscle	β2	Constricts bronchiolar smooth muscle	M3
Male sex organs	Ejaculation	α	Erection	M
Bladder	Relaxes bladder wall	β2	Contracts bladder wall	M3
	Constricts sphincter	α1	Relaxes sphincter	M3
Sweat glands	↑ sweating	M (sympathetic cholinergic)	-------------	
Eye	Dilates pupil (mydriasis)--(far vision)	α1	Constricts pupil (miosis)--(near vision)	M
Kidney	↑ renin secretion	β1	----------------	
Fat cells		β1	----------------	

Types of Sensory Receptors

Receptor Type	Fiber Type	Senses
Free Nerve Endings	C—slow, unmyelinated fibers Aδ—fast, myelinated fibers	• Pain • Temperature
Meissner Corpuscles	Large, myelinated fibers; adapt quickly	• Dynamic (velocity) • Fine/light touch • Position sense
Pacinian Corpuscles	Large, myelinated fibers; adapt quickly	• Pressure • Vibration
Merkel Discs	Large, myelinated fibers; adapt slowly	• Pressure • Deep static touch (e.g., shapes, edges). • Position sense (location)
Ruffini Corpuscles	Adapt slowly	• Pressure • Slippage of objects along surface of skin, • Joint angle change

Electromagnetic Receptors

- Which detect light on retina of eye: rods and cones

Chemoreceptors

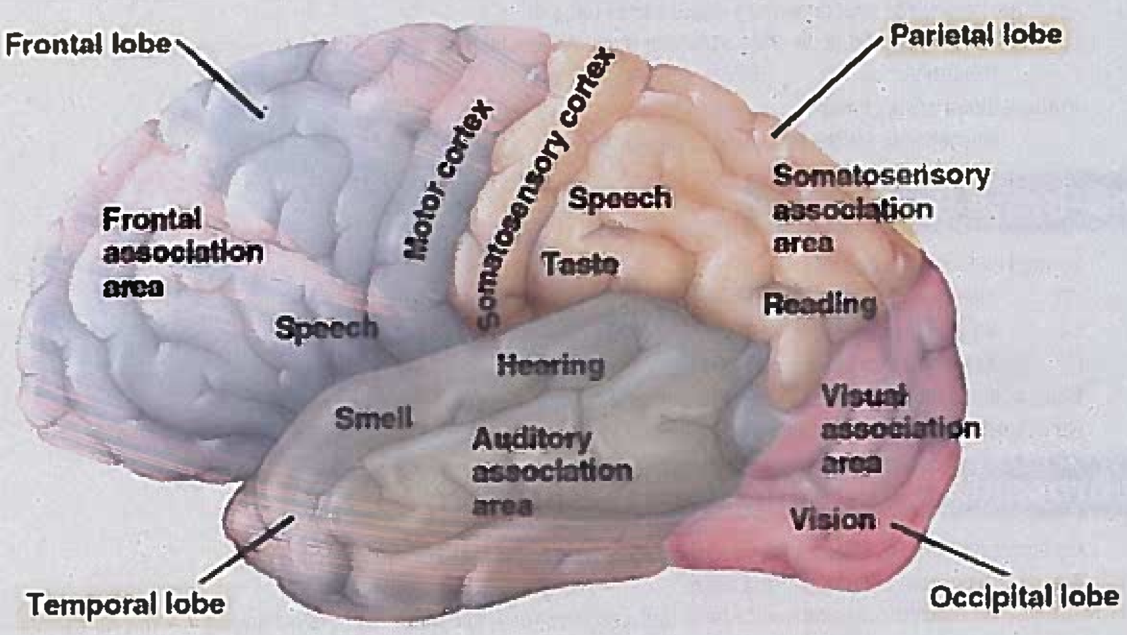
- For taste: receptors of taste buds
- For smell: receptor of olfactory epithelium
- For arterial Oxygen: receptor for aortic and carotid bodies
- For osmolality: neurons in or near supraoptic nuclei

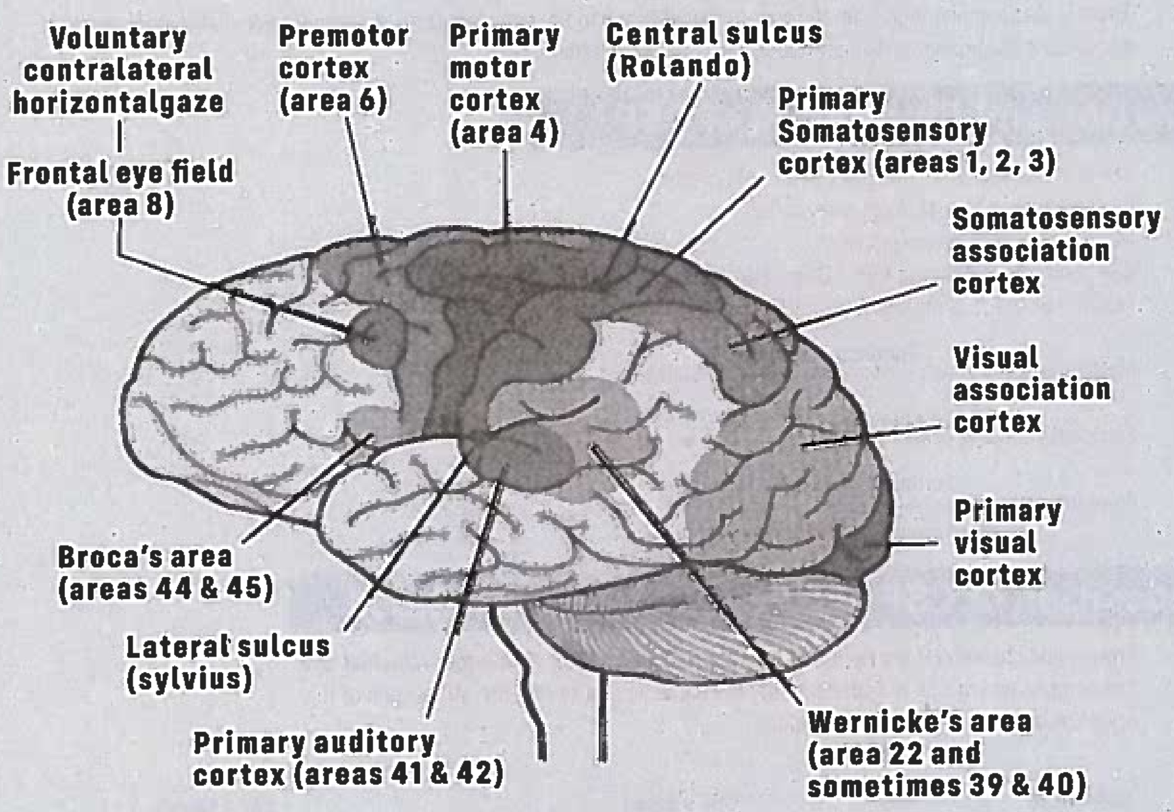
Nerve Fiber Types

- General fibers are classified into A,B and C
- A, B are myelinated and Fast, while C is unmyelinated and slow
- The group A is further subdivided into alpha(α), beta(β), gamma(γ), delta(δ)
- As we go down from A to C , the diameter and velocity decreases

General Fiber Type	Sensory Fiber Type	Example	Diameter	Conduction Velocity
Aα	Ia	Muscle spindle	Largest	Fastest
	Ib	Golgi tendon organs		
Aβ	II	Touch and pressure	Medium	Medium
Aγ		Intrafusal fibers		
Aδ	III	Touch, pressure, temperature, and pain **(FAST)**	Small	Medium
B		Preganglionic autonomic fibers	Small	Medium
C (unmyelinated)	IV	Postganglionic autonomic, temperature and Pain **(SLOW)**	Smallest	Slowest

Functional Areas of Cerebral Cortex





- Motor speech (Broca's) area = (44, 45).
- Primary auditory cortex = (41, 42).
- Associative auditory cortex (Wernicke's area) = (22).
- Principal visual cortex = (17).
- Principal sensory areas = (3, 1, 2).
- Principal motor area = (4).
- Premotor area = (6) (part of extrapyramidal circuit)
- Frontal eye movement and pupillary change area = (8)

Motor Cortex

- Premotor cortex and supplementary motor cortex (area 6)
  - Responsible for generating a plan for movement, which is transferred to the primary motor cortex for execution.
- Primary motor cortex (area 4)
  - Responsible for the execution of movement

Blood-Brain Barrier

- Formed by 3 structures:
  - Tight junctions between non-fenestrated capillary endothelial cells
  - Basement membrane
  - Astrocyte foot processes
- Glucose and amino acids cross slowly by carrier mediated transport mechanisms.
- Nonpolar/lipid-soluble substances cross rapidly via diffusion.

Cerebrospinal Fluid and Ventricular System

- Cerebrospinal fluid (CSF) is a clear, colorless body fluid found in the brain and spinal cord.
- It acts as a cushion or buffer for the brain.
- The CSF occupies the subarachnoid space (between the arachnoid mater and the pia mater) and the ventricular system around and inside the brain and spinal cord.
- There is also a connection from the subarachnoid space to the bony labyrinth of the inner ear via the perilymphatic duct where the perilymph is continuous with the cerebrospinal fluid.

Formation and Circulation of CSF

- CSF is made by ependymal cells of choroid plexus
- it is reabsorbed by arachnoid granulations
- Drains into Dural venous sinuses.
- CSF is produced at a rate 450-500mL per day
- Majority of CSF is produced from within the two lateral ventricles
- From lateral ventricles $\xrightarrow{\text{Foramina of Monro}}$ 3rd ventricle
- From 3rd ventricle $\xrightarrow{\text{cerebral aqueduct of Sylvius}}$ 4th ventricle
- From 4th ventricle $\xrightarrow[\text{Foramina of Magendie--Medial}]{\text{Foramina of Luschka--Lateral}}$ into subarachnoid space

Composition of CSF and Comparison with Blood

- Protein and cholesterol are excluded from the CSF because of their large molecular size.
- The composition of CSF is approximately the same as that of the interstitial fluid of the
- brain but differs significantly from blood

CSF=Blood	CSF < Blood	CSF > Blood
Na+	K+	Mg2+
Cl-	Ca2+	Creatinine
HCO3-	Glucose	
Osmolarity	Cholesterol	

Hypothalamus

Area	Function	Notes
Lateral Area	Stimulates Hunger	Stimulated by Ghrelin (Gains appetite) Inhibited by Leptin (Lowers appetite)
Ventromedial Nucleus	Inhibits appetite	VIP – (Ventromedial Inhibits Appetite) Craniopharyngioma →Destruction occurs in leading to Hyperphagia.
Anterior Hypothalamus	Cooling, parasympathetic.	A/C → Anterior is for Cooling
Posterior Hypothalamus	Heating, sympathetic.	
Suprachiasmatic Nucleus	Circadian rhythm.	You need sleep to be charismatic (chiasmatic).
Supraoptic Nuclei	Synthesize ADH	
Paraventricular Nuclei	Synthesizes oxytocin	

Thalamus

- Major relay for all ascending sensory information except olfaction.

Nuclei	Function (senses)	Notes
Lateral Geniculate Nucleus	Vision	Lateral = Light
Medial Geniculate Nucleus	Hearing	Medial = Music
Ventral Postero-Lateral Nucleus	Vibration Pain, Pressure, Proprioception, Light touch temperature	Medial = Music
Ventral Postero-Medial Nucleus	Face sensation Taste	Makeup goes on the Face

Sleep Physiology

- Sleep cycle is regulated by the circadian rhythm, which is driven by suprachiasmatic nucleus (SCN) of hypothalamus.
- Two stages: rapid-eye movement (REM) and non-REM.

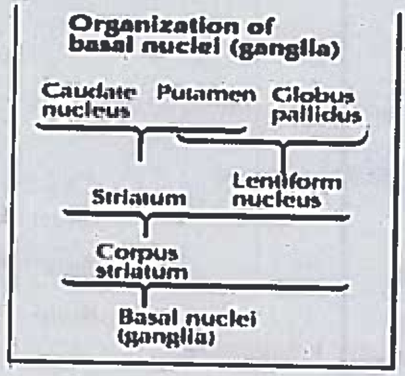
Non-REM (75%)	REM (25%)
In Non-REM sleep following occurs • Sleepwalking • Night terrors • Bedwetting (enuresis) • Bruxism	Most dreams occur during REM sleep. REM sleep is characterized by • Eye movements • Loss of muscle tone • Pupillary constriction • Penile erection. • Nightmares • ↑ ACh
	Depression ↑ total REM sleep
	Alcohol, benzodiazepines, and barbiturates Norepinephrine ↓ REM sleep.

EEG WAVE CHANGES

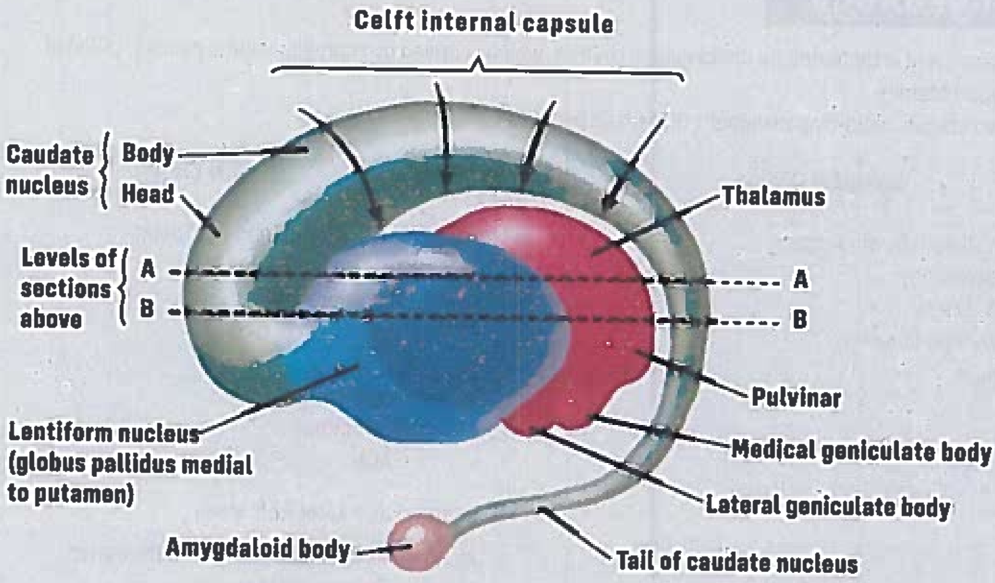
• Awake (Eyes Open)	Beta waves	Mnemonic:
• Awake (Eyes Closed	Alpha waves	At night, **BAT D**rink **B**lood
• Non- REM Sleep (Stage-1 Light Sleep)	Theta waves	
• Non- REM Sleep (Stage-2- Deep	Delta waves	
• REM Sleep	Beta waves	

Basal Ganglia

- Important in voluntary movements and making postural adjustments.
- Modulates thalamic outflow to the motor cortex to plan and execute smooth movements
- Consists of the striatum, Globus pallidus and caudate nuclei
  - **Striatum** = Putamen (motor) + Caudate (cognitive).
  - **Lentiform** = Putamen + Globus pallidus



- Many synaptic connections are inhibitory and use GABA as their neurotransmitter
- The striatum communicates with the thalamus and the cerebral cortex by two opposing pathways.
  - Indirect pathway is, overall, inhibitory.
  - Direct pathway is, overall, excitatory.
- Connections between the striatum and the substantia nigra use dopamine as their neurotransmitter.



Interrelationship of thalamus, lentiform nucleus, caudate nucleus, and amygdaloid body (schema): left lateral view

Cerebrovascular Diseases

Infarcts

Ischemic stroke	• Acute blockage of vessels → disruption of blood flow and subsequent ischemia → causing Liquefactive necrosis.
	• it may be due to
	  ◦ Thrombosis → more common, most common site is middle cerebral artery
	  ◦ Embolism → less common, most common site is middle cerebral artery
	• **Hippocampus is most vulnerable** to ischemic hypoxia (**"vulnerable hippos"**).

Transient Ischemic Attacks (TIAs)	• These brief episodes of impaired neurologic function are caused by a temporary disturbance of cerebral circulation. • TIAs are not associated with permanent damage, but are considered precursors to more serious occlusive events. • TIA usually last only a few minutes but may persist for up to 24 hours (but not more than 24 hours)
NICE GUIDLEINES on Stroke	See below

<u>Selected points relating to the management of acute stroke include:</u>

- **Blood glucose, hydration, oxygen saturation and temperature** should be maintained within normal limits
- **Blood pressure should not be lowered in the acute phase** unless there are complications e.g. Hypertensive encephalopathy
- **Aspirin 300mg** orally or rectally should be given as soon as possible if a hemorrhagic stroke has been excluded
- With regards to atrial fibrillation, the RCP state: '**anticoagulants** should not be started until brain imaging has excluded hemorrhage, and usually **not until 14 days** have passed from the onset of an ischemic stroke'
- If the **cholesterol is > 3.5 mmol/l** patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to risk of haemorrhagic transformation

<u>Thrombolysis:</u>

- Thrombolysis should only be given if:
  - It is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
  - Hemorrhage has been definitively excluded (i.e. Imaging has been performed)
- **Alteplase is currently recommended by NICE.**
- **<u>Contraindications to thrombolysis:AbsoluteRelative</u>**

Absolute	Relative
• Previous intracranial haemorrhage	• Concurrent anticoagulation (INR >1.7)
• Intracranial neoplasm	• Hemorrhagic diathesis
• Suspected subarachnoid haemorrhage	• Active diabetic hemorrhagic retinopathy
• Stroke or traumatic brain injury in preceding 3 months	• Suspected intracardiac thrombus
• Seizure at onset of stroke	• Major surgery / trauma in preceding 2 weeks
• Lumbar puncture in preceding 7 days	
• Oesophageal varices	
• Active bleeding	
• Gastrointestinal haemorrhage in preceding 3 weeks	
• Pregnancy	
• Acute pancreatitis	
• Uncontrolled hypertension >200/120mmHg	

Intracranial Haemorrhage

Epidural hematoma

MMA

Lens shaped

EPIDURAL
- Rupture of middle meningeal artery (branch of maxillary artery), often 2° to skull fracture.
- Lens shaped (biconvex / lentiform) hematoma.
- Involving the pterion (thinnest area of the lateral skull)—temporal lobe
- **Lucid interval** (temporary improvement in a patient's condition after a traumatic brain injury, after which the condition deteriorates)
- **CN III palsy.**

Subdural hematoma

banana shaped

SUBDURAL
- **Rupture of bridging veins/great cerebral vein/diploic vein**
- **Crescent-shaped hematoma.**
- Most commonly secondary to trauma **e.g., old person/alcohol falling over**
- Most commonly occur around the frontal and parietal lobes
- Risk factors include **old age, alcoholism and anticoagulation**
- Features:
  - Headache
  - **Classically fluctuating conscious level**
  - Raised ICP

Subarachnoid hemorrhage

SUBARACHNOID
- Bleeding due to trauma, or rupture of an aneurysm (such as a saccular aneurysm) or arteriovenous malformation.
- Patients complain of "worst headache of my life." + Neck stiffness on examination
- Investigations:
  - CT: negative in 5%
  - LP:
    - Done after 12 hrs (in Pass-medicine) and 4-10 days in First aid (allowing time for xanthochromia to develop)
    - If the CSF examination revealed xanthochromia, or there was still a high level of clinical suspicion, **then cerebral angiography would be the next step.**
  - Cerebral angiography:
- Complications:
  - ↑ Risk of developing communicating and/or obstructive hydrocephalus.
  - Typically the development of DCI (delayed cerebral ischemia) starts **on day 3 after the inital SAH and is maximal at days 5-14 and resolves on day 21.**
- Treatment: Nimodopine (60mg 4 hrly if BP allows) used to prevent/reduce vasospasm.

Intraparenchymal hemorrhage
- Most commonly caused by systemic hypertension.
- May be 2° to reperfusion injury in ischemic stroke.
- Charcot-Bouchard aneurysms may be sites of hemorrhagic rupture.
- Typically occurs in basal ganglia and internal capsule

Epidural Hematoma

bone

Subdural Hematoma

Head Injury

- NICE has strict and clear guidance regarding which adult patients are safe to discharge and which need further CT head imaging.

CT head **immediately**	• GCS < 13 on initial assessment • GCS < 15 at 2 hours post-injury • Suspected open or depressed skull fracture. • Any sign of basal skull fracture (haemotympanum, 'panda' eyes, Battle's sign, CSF fluid leakage from the ear or nose). • Post-traumatic seizure. • Focal neurological deficit. • more than 1 episode of vomiting

CT head scan **within 8 hours** of the head injury	For adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:
	• Age 65 years or older
	• Any history of bleeding or clotting disorders
	• If a patient is on warfarin who has sustained a head injury with no other indications
	• Dangerous mechanism of injury:
	    · A pedestrian or cyclist struck by a motor vehicle,
	    · An occupant ejected from a motor vehicle or
	    · A fall from a height of greater than 1 metre or 5 stairs
	• 30 minutes' retrograde amnesia of events immediately before the head injury

Battle's Sign & Raccoons Eye

Battles sign	Raccons eye or Panda eyes (called panda eyes in England and Ireland)
• Bruising over the mastoid • Indication of fracture of middle cranial fossa • This sign will take at least one day to appear	• Periorbital ecchymosis • Indication of fracture of anterior cranial fossa **(basal skull fracture)** • Atleast one day to develop (mainly 2-3 days)

B Raccoon's eyes

C Battle's sign

Effect of Strokes In Relation to Artery

Artery	Features

Middle cerebral artery	• Contralateral paralysis and sensory loss
	• Contralateral homonomous hemiriopia
	• Aphasia
	  ◦ Temporal lobe (Wernicke area) sup. temp. gyrus
	  ◦ Frontal lobe (Broca area). inf. frontal. gyrus.

Anterior cerebral artery	• Contralateral paralysis and sensory loss
Anterior spinal artery	• Contralateral paralysis ↓contralateral proprioception. • Ipsilateral hypoglossal dysfunction→ tongue deviates ipsilaterally • e.g. on right side artery lesion → tongue deviated towards right

Posterior inferior cerebellar artery	• Lateral medullary syndrome (aka Wallenberg syndrome, posterior inferior cerebellar artery syndrome "PICA")
	  ◦ Ipsilateral →Ataxia, nystagmus
	  ◦ Ipsilateral →facial pain and temperature loss
	  ◦ Contralateral →pain and temperature loss
	• Dysphagia, hoarseness, ↓gag reflex, Vomiting, vertigo, nystagmus Ipsilateral Horner syndrome

Anterior inferior cerebellar artery	• Lateral pontine syndrome
	  ◦ Ipsilateral →Ataxia, nystagmus
	  ◦ Ipsilateral → **facial paralysis** (↓ lacrimation, ↓ salivation, ↓ taste from anterior 2/3rd of tongue) **and deafness**
	  ◦ Contralateral → pain and temperature loss
	• Ipsilateral Horner syndrome

Posterior cerebral artery	• Contralateral hemianopia with macular sparing
Retinal/ophthalmic artery	• Amaurosis fugax (painless temporary loss of vision in one or both eyes)

- **Note**
  - The only feature that differentiates the middle cerebral artery syndrome from the carotid artery syndrome is amaurosis fugax.
  - Amaurosis fugax, which is unilateral transient loss of vision that develops over seconds, remains for up to 5 minutes and resolves over 10-20 minutes.

Aphasia

- Information is transferred between the two hemispheres of the cerebral cortex through the corpus callosum.
- The right hemisphere is dominant in facial expression, body language, and spatial tasks.
- The left hemisphere is usually dominant with respect to language, even in left-handed people.
- Lesions of the left hemisphere cause aphasia.
- Aphasia results from damage in → temporal lobe

Broca aphasia Mnemonic: Broca's =Broken mouth	• Also known as Motor aphasia Nonfluent aphasia, expressive aphasia • Patient can't speak properly but can understand written and spoken language • Area 44 and 45 • Broca's area located in inferior frontal gyrus
Wernicke aphasia Mnemonic: Wernicke is Wordy but makes no sense.	• Also known as sensory aphasia, Fluent aphasia, receptive aphasia • Patient can speak, but can't understand spoken and written language • Area 22 • Wernicke's area located in superior temporal gyrus
Global aphasia	• Lesion in Arcuate fasciculus • Broca and Wernicke areas affected (all areas).

Meningitis

- Clinical manifestations include fever, headache, prostration, and nuchal rigidity
- Organisms
  - Viral causes of meningitis
    - Enteroviruses (especially coxsackievirus)
    - HSV-2 (HSV-1 = encephalitis),
    - HIV,
    - West Nile virus (also causes encephalitis),
    - VZV.
    - In HIV Cryptococcus spp.

Newborn (0–6 Mo)	Children (6 Mo–6 YR)	6–60 YR
• Group B streptococci • E. coli • Listeria	• S. pneumoniae • N. meningitidis • H. influenzae type B • Enteroviruses	• S pneumoniae • N meningitidis (#1 in teens) • Enteroviruses • HSV

CSF Findings in Meningitis

	Opening Pressure	Cell Type	Protein	Glucose
Normal values	10-20 cm H_2O	WCC 0-5 cells/μL	20-40 mg/dL	45-80 mg/dL (less than 2/3[rd] of blood glucose)
Bacterial	↑	↑PMN'S	↑ (> 1g/L)	↓ (1/2 of plasma)
Fungal/TB	↑	↑LYMPHOCYTES	↑ (> 1g/L)	↓ (1/2 of plasma)
Viral	↑/Normal	↑LYMPHCYTES	↑/Normal	Normal or 80% of plasma glucose • Remember: Mumps and herpes encephalitis unusally causes a low glucose level

Hydrocephalous

- This condition denotes increased volume of cerebrospinal fluid (CSF) within the cranial cavity.

Communicating Hydrocephalus	• Free flow of CSF between the ventricles and the subarachnoid space
Non-Communicating Hydrocephalus	• Obstructed flow of CSF from the ventricles to the subarachnoid space
Hydrocephalus Ex Vacuo	• Mimics hydrocephalous • Appearance of ↑CSF on imaging, but is actually due to decreased brain tissue and neuronal atrophy (e.g., Alzheimer disease)

Degenerative Diseases

Alzheimer Disease	• Associated with the following altered proteins: ◦ ApoE2: ↓risk of sporadic form ◦ ApoE4: ↑ risk of sporadic form ◦ APP, presenilin-1, presenilin-2: familial forms (10%) with earlier onset • ↓ Ach • Most common cause of dementia in elderly. • Down syndrome patients have ↑risk of developing Alzheimer disease • **Widespread cortical atrophy**→ Narrowing of gyri and widening of sulci. • Morphologic abnormalities ◦ Senile plaques ◦ Amyloid Angiopathy→ **β-amyloid deposition** in and about vessels ◦ **Neurofibrillary tangles** ◦ Intracellular, **hyper-phosphorylated tau protein** • Management: ◦ **Acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine)**
Parkinson Disease	• ↓ Dopamine • This disease appears clinically most often after 50 years of age • Loss of dopaminergic neurons (i.e. depigmentation) of substantia nigra • Damaged cells contain highly characteristic eosinophilic intracytoplasmic inclusions (Lewy bodies). • Clinical features: (Mnemonic: Parkinson **TRAPS** your body) ◦ **T**remor (pill-rolling tremor at rest) ◦ **R**igidity (cogwheel) ◦ **A**kinesia (or bradykinesia) ◦ **P**ostural instability ◦ **S**huffling gait • Causes: ◦ Idiopathic (most common) ◦ Trauma, especially repeated trauma, as may occur in boxers. ◦ Drugs and toxins, especially dopamine antagonists such as **MPTP (methyl-phenyltetrahydropyridine)** →a contaminant in illegal street drugs. ◦ **Shy-Drager syndrome** →parkinsonism with autonomic dysfunction and orthostatic hypotension • Management: ◦ Dopamine receptor agonists (Bromocriptine, cabergoline) ▪ Side effects: pulmonary, retroperitoneal and cardiac fibrosis ◦ Levodopa ▪ Usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of L-dopa to dopamine ▪ Reduced effectiveness with time (usually by 2 years) ◦ Monoamine Oxidase-B (MAO-B) inhibitors e.g. Selegiline
Pick Disease (Frontotemporal dementia)	• This disorder clinically resembles Alzheimer disease • **EEG is relatively normal** by contrast with Alzheimer's disease. • It is more frequent in women. • Characteristics include marked cortical atrophy, especially of the **temporal and frontal lobes**; swollen neurons; and **Pick bodies** (round intracytoplasmic inclusions consisting of neurofilaments)
Lewy body dementia	• Dementia and visual hallucinations ("ha**Lewy**cinations") parkinsonian features • Intracellular Lewy bodies primarily in cortex • Diagnosis: ◦ Single-photon emission computed tomography (SPECT) is aka as DaTscan. • Management: **Rivastigmine**

Tumors

- In adults, the majority of intracranial tumors are supratentorial.
- In children, the majority of intracranial tumors are infratentorial.
- CNS tumors are the second most common form of malignancy in children (only leukemia is more frequent).

Adult Primary Brain Tumors

- Most common are glioblastoma multiforme (Astrocytoma) > meningioma > acoustic neuroma

Glioblastoma multiforme (grade IV astrocytoma)	• Common, highly malignant 1° brain tumor with ~1-year median survival. Found in cerebral hemispheres • Can cross corpus callosum ("butterfly glioma").
Oligodendroglioma	• This neoplasm presents as a slow-growing tumor in the middle-age group and typically arises in the cerebral hemispheres • Closely packed cells with large round nuclei surrounded by a clear halo of cytoplasm (**"fried egg" appearance**) • Foci of calcification
Meningioma	• Second most common primary intracranial neoplasm • The neoplasm originates in arachnoidal cells of the meninges; the tumor is external to the brain and can often be successfully removed surgically. • This neoplasm occurs most frequently in the cerebral hemispheres and the parasagittal region • Histologic characteristics include a whorled pattern of concentrically arranged spindle cells and laminated calcified Psammoma bodies.
Hemangioblastoma	• This neoplasm occurs most frequently in the cerebellum. • It may be associated with similar lesions in the retina and other organs as part of von Hippel-Lindau disease. • It sometimes produces erythropoietin, leading to secondary polycythemia
Schwannoma (neurilemmoma)	• This benign, slowly growing encapsulated tumor arises from Schwann cells. • When intracranial, it is most frequently localized to the 8th cranial nerve (acoustic neuroma, acoustic Schwannoma) • Acoustic neuroma is the third most common primary intracranial neoplasm • It also originates frequently in posterior nerve roots and peripheral nerves.

Childhood Primary Brain Tumors

- The most common primary intracranial tumors in children are cerebellar astrocytoma and medulloblastoma.

Pilocytic/ cerebellar (low-grade) astrocytoma	• Usually well circumscribed. In children, most often found in posterior fossa (cerebellum). • Benign; good prognosis. • Rosenthal fibers—eosinophilic
Medulloblastoma	• Medulloblastoma Most common malignant brain tumor in childhood. • Commonly involves cerebellum • Can compress 4th ventricle, causing Non-communicating hydrocephalus
Ependymoma	• Ependymal cell origin. Most commonly found in 4th ventricle • Can cause hydrocephalus. Poor prognosis.
Craniopharyngioma	• Derived from remnants of Rathke pouch. • May be confused with pituitary adenoma (both cause bitemporal hemianopia)

Seizures and Epilepsy

- Seizures = it is an abnormal paroxysmal, excessive discharge of CNS neurons
- Epilepsy = it is defined as condition of recurrent seizures due to a chronic underlying process
- Status epilepticus = seizure lasting (> 5-30 min) or recurring seizures without the patient regaining awareness between attacks.

Causes: (VITAMIN-G)

- Vascular (e.g. stroke, arteriovenous malformations), Infection (e.g. meningitis, encephalitis, abscess), Trauma, Autoimmune, Metabolic (e.g. Hyponatremia, hypoglycemia, hypocalcemia, hypoxia), Idiopathic, Neoplasm, Genetic & development

Classification

Partial (focal) seizures

- Arise from discrete, focal portion of brain (one part of cortex)

Simple Partial Seizures	Complex Partial Seizures
it begins as jerking on one side of the mouth or in one hand	it begins as repetitive blinking of eye, smacking of lips and cannot interact normally with people
No loss of consciousness	Impairment of consciousness
No Post-ictal confusion	Post ictal confusion
Jacksonian seizure: • Also known as focal partial motor seizure • It begins as jerking on one side of mouth or in one hand, sometimes spreading to involve the entire side	**Temporal lobe epilepsy:** • Presents with the sensation of **déjà vu** (undue familiarity) or **Jamais vu** (an unreal feeling) and can progress to hallucinations and altered conscious level.
Todd's palsy: • It refers to paralysis of involved limb after a seizure with complete recovery within 24 hours	

Generalized seizures

- Arise diffusely from both cerebral hemisphere simultaneously.
- **Generalized tonic-clonic seizure (grand mal):**
  - Alternating stiffening and movement with loss of consciousness
- **Absence (Petit mal)**
  - In this there is loss of consciousness but no loss of postural tone (e.g. The person seems to be day dreaming)
  - On EEG---3 per second spike and wave electrical activity
- **Myoclonic:**
  - Quick, repetitive jerks
- **Atonic:**
  - "Drop" seizures (falls to floor); commonly mistaken for fainting

Status Epilepticus

- **Definition:**
  - It is defined as a continuous seizures lasting for at least 30 minutes, 1 or two or more discrete seizures, between which the patient does not recover consciousness.
- **Cause:**
  - Idiopathic (no previous CNS insult)
  - Sudden withdrawal of anti-epileptic drugs (most common cause)
  - Initial presentation of epilepsy
  - Sleep deprivation in epileptic patient.

	• Intercurrent illness • Sever anoxic encephalopathy • Electrolyte abnormality • **Treatment:** General measures: • Ensure airway is patent. Give 02 at 10L/min • Place patient in semi-prone position to decrease risk of aspiration. • Intravenous access, start normal saline infusion • Draw blood for CBC, UCE, serum calcium, glucose, serum and urine toxicology screen Pharmacological treatment • Administer benzodiazepine IV or rectally. (Lorazepam is preferred because of long duration) • If the patient does not respond, the regime may be repeated after 5-10 minutes • If seizures recur or fail to respond after 30 minutes a parenteral antiepileptic agent should be started. • Intravenous phenytoin/Fosphophenytoin is usually used and is given as a loading dose of 18 mg/kg • Adverse effects: CNS depression and cardiac arrhythmias • If seizures continue = general anaesthesia (propofol, or thiopental) + assisted ventilation. • Once seizure is controlled= long-term anticonvulsant therapy (sodium valproate, or phenytoin) + investigation of cause

Treatment

Epilepsy type	Preferred 1st line Agent	Other 1st line agent	
Partial seizures	Carbamazepine (Phenobarbital in neonates)	Lamotrigine Sodium valproate	
Tonic clonic seizure	Sodium valproate	Lamotrigine	
Absence seizures	Ethosuximide	Sodium valproate	Carbamazepine may exacerbate
Myoclonic seizures	Sodium valproate	Clonazepam	
Status epilepticus	benzodiazipines(e.g. diazepam)	Clonazepam	
Epilepsy in pregnancy and breast feeding	• All women thinking about becoming pregnant should be advised to take **folic acid 5mg** per day well **before pregnancy to minimise the risk of neural tube defects** • Aim for monotherapy • There is no indication to monitor antiepileptic drug levels	• Carbamazepine: **Most safe** • Sodium valproate: **contraindicated. neural tube defects** • Phenytoin: **cleft palate, clotting disorders** (give vit k) • Lamotrigine: dose needs to be ↑ in pregnancy • Breast feeding: **safe** (except barbiturates)	

Difference between Upper and Lower Motor Neuron Lesions

- Lower motor neuron = everything lowered (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes).
- Upper motor neuron = everything up (↑tone, ↑reflexes, Upgoing toes).
- Remember Babinski sign → big toe goes upward, seen normally in infants, and in UMN lesions

	UMN lesion	LMN lesion
Weakness	+	+
Atrophy	-	+
Tone	↑	↓
Reflexes	↑	↓
Fasciculations	-	+
Babinski	+	-
Spastic paresis	+	-
Flaccid paralysis	-	+
Clasp knife spasticity	+	-

Neuroleptic Malignant Syndrome (NMS)

Status Epilepticus	• A rare but dangerous condition seen in patients taking antipsychotic medication
Etiology	• Caused by a sudden reduction in dopamine activity, either from blockade of dopamine receptors or withdrawal of dopaminergic agents. • Causative drugs : typical antipsychotics ◦ Haloperidol, pimozide, trifluoperazine, fluphenazine, thioridazine, chlorpromazine
Features	Mnemonic: **Malignant FEVER:** ◦ **M**yoglobinuria ◦ **F**ever ◦ **E**ncephalopathy ◦ **U**nstable **V**itals ◦ ↑ **E**nzymes ◦ Muscle **R**igidity
Treatment	• IV fluids to prevent renal failure • Reduction of body temperature with antipyretics • **Dantrolene, D2 agonist (e.g., bromocriptine).**

Idiopathic Intracranial Hypertension/ Pseudotumor Cerebri)

Definition	• ICP with no apparent cause on imaging (e.g., hydrocephalus, obstruction of CSF outflow).
Risk factors	• **Female gender, obesity, vitamin A excess,** tetracycline, danazol.
Findings	• Headache • Diplopia (usually from CN VI palsy) • No change in mental status. • Papilledema • Lumbar puncture reveals → **↑opening pressure (more than 20 cmH2O)** and provides headache relief.
Treatment	• Weight loss • Diuretics: Acetazolamide • Invasive procedures: for refractory cases ◦ Repeated lumbar puncture ◦ CSF shunt placement (Lumboperitoneal shunt—treatment of choice) ◦ Optic nerve sheath fenestration surgery

Migraine

- Pulsating headache pain with nausea, photophobia, or phonophobia.
- It can occurs as aura or without aura
- Aura: An aura is a perceptual disturbance, manifests as the perception of a strange light, an unpleasant smell, or confusing thoughts or experiences
- **Clinical features:** Mnemonic **POUND**
  - **P**ulsatile, **O**ne-day duration, **U**nilateral, **N**ausea, **D**isabling
- **Diagnosis:**
  - Diagnosis for migraine with aura is easy
  - Diagnosis for migraine without aura ---- The International Headache Society diagnostic criteria

Point	Criteria
A	At least 5 attacks fulfilling criteria B-D
B	Headache attacks lasting **4-72 hours*** (untreated or unsuccessfully treated)
C	Headache has at least two of the following characteristics: • Unilateral location • Pulsating quality (i.e., varying with the heartbeat) • Moderate or severe pain intensity • Aggravation by/or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D	During headache at least one of the following: • Nausea and/or vomiting* • Photophobia and phonophobia
E	Not attributed to another disorder

- **Treatment:**

Acute attacks	• **First line treatment:**
	  • oral sumatriptan (5-HT receptor agonists) + an NSAID **"OR"**
	  • an oral sumatriptan + paracetamol
	• **2nd line treatment :** if above measures not effected or tolerated
	  • a non-oral preparation of metoclopramide* **OR** prochlorperazine **PLUS**
	  • a non-oral NSAID **OR** triptan

Prophylaxis	• Prophylaxis should be given if patients are experiencing **2 or more attacks per month**
	• **1st line treatment:**
	  • Topiramate or
	  • Propranolol (Other drugs are CCB's, SSRI (Amitriptyline))
	• **2nd line treatment:**
	  • **Gabapentin**
	  • **Riboflavin 400 mg** once a day may be effective in reducing migraine frequency and intensity
	• **Special considerations:**
	  • **IF pregnant: use propranolol (Topiramate is teratogenic** & ↓ effectiveness of hormonal contraceptives)
	  • For women with predictable menstrual migraine recommend either:
	    • Frovatriptan (2.5 mg twice a day) or
	    • Zolmitriptan (Zomig)(2.5 mg twice or three times/day)
	  • Pizotifen is no longer recommended. Adverse effects such as weight gain & drowsiness are common

Migraine in pregnancy, contraception and other hormonal factors	• **Active Migraine during pregnancy** ◦ 1st line---paracetamol 1g ◦ 2nd line ----aspirin 300mg or ibuprofen 400mg in the first and second trimester • **Migraine and the combined oral contraceptive (COC) pill** ◦ If patients have migraine with aura then the COC is absolutely contraindicated due to an increased risk of stroke • **Migraine and hormone replacement therapy (HRT)** ◦ Safe to prescribe HRT for patients with a history of migraine but it may make migraines worse

Multiple sclerosis

Definition	• Autoimmune inflammation and demyelination of CNS (brain and spinal cord).
Epidemiology	• Most often affects women in their 20s and 30s
Clinical features	• Symptoms may exacerbate with increased body temperature (eg, hot bath, exercise). • Relapsing and remitting is most common clinical course. • Charcot triad of MS is a **SIN:** ◦ **S**canning speech ◦ **I**ntention tremor (also **I**ncontinence and **I**nternuclear ophthalmoplegia "INO") ◦ **N**ystagmus • Other features: ◦ Visual: ▪ Optic neuritis (sudden loss of vision resulting in Marcus Gunn pupils) ▪ Optic atrophy ▪ INO ◦ Sensory: ▪ Pins/needles and numbness, Sensory symptoms lasting for weeks are common in MS ▪ Trigeminal neuralgia ▪ Lhermitte's syndrome: Neck flexion may precipitate sensation of electric shock running down spine ◦ Motor: ▪ Spastic weakness: most commonly seen in the legs, ▪ Intentional tremors ▪ Urinary incontinence
Investigations	• Diagnosis requires demonstration of lesions **disseminated** in time and space • **MRI (Gold standard)** ◦ High signal T2 lesions, **periventricular plaques** ◦ CSF: ▪ **Oligoclonal bands** (and not in serum) ▪ Increased intrathecal synthesis of IgG ◦ Visual evoked potentials: VEP ▪ Delayed, but well preserved waveform
Management	• There is no cure. • Treatment is focused at reducing the frequency and duration of relapses. • Acute relapse: High dose IV steroids (methylprednisolone for 3-5 days) • Disease modifying therapies (β-interferon, glatiramer, natalizumab) ◦ β-interferon: (Criteria for use) ▪ Has had more than two separate episodes within the last two years ▪ Is more than 18-years-old, and ▪ Can walk more than 100 metres.

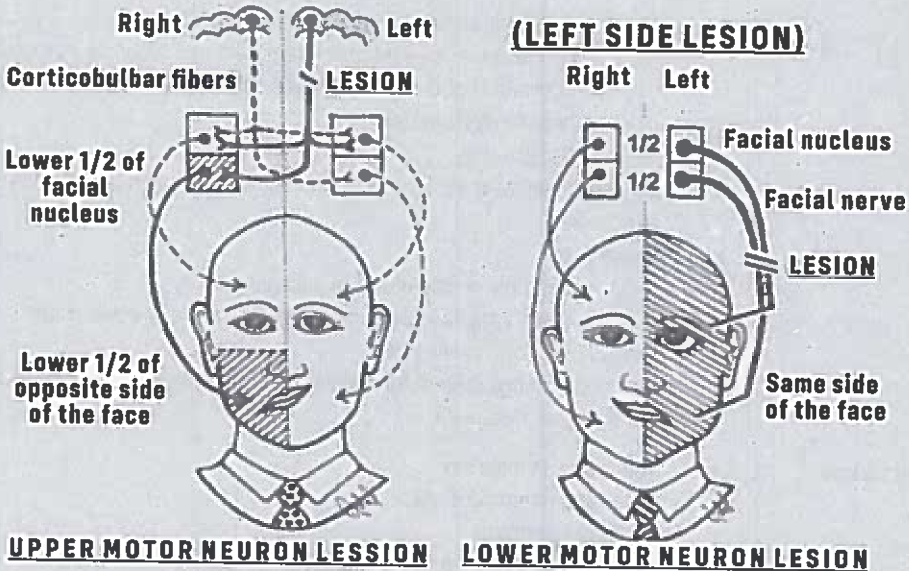
	- β-interferon 1a--- relapsing-remitting MS - β-interferon 1b--- relapsing remitting and secondary progressive - Contraindications: **uncontrolled epilepsy, severe clinical depression, hepatic dysfunction** - Natalizumab: • Mitoxantrone: reserved for high frequency relapse rates unresponsive to beta interferon • Spasticity: - first line → Baclofen and gabapentin - Other options include → diazepam, dantrolene and tizanidine • Pain: (TCAs, anticonvulsants) • Plasma exchange: severe function or life threatening relapses not responding to conventional treatment.
Good prognostic factors	• Young age, Female sex • Relapsing remitting disease • Sensory symptoms • Long interval between first 2 relapses

Herpes Simplex Encephalitis

Features	• Fever, headache, psychiatric symptoms, seizures, vomiting, focal features (e.g. aphasia) • **HSV-1** responsible for **95%** of cases in adults • typically affects **temporal** and **inferior frontal** lobes
Investigation	• PCR for HSV: **diagnostic in 95%** • CT: - Medial temporal and inferior frontal changes (e.g. **petechial haemorrhages**) - normal in one-third of patients • MRI is better than CT • EEG pattern: lateralised periodic discharges at 2 Hz
Treatment	• **Intravenous acyclovir**
Prognosis:	• The prognosis is dependent on whether acyclovir is commenced early. • If treatment is started promptly the mortality is 10-20%. • Left untreated the mortality approaches 80%
HINT	• The virus characteristically affects the temporal lobes - questions may give the result of imaging or describe temporal lobe signs e.g. aphasia

Facial Nerve Lesions

Upper Motor Neuron Lesion	Lower Motor Neuron Lesion
• Destruction of motor cortex or connection between motor cortex and facial nucleus in pons	• Destruction of facial nucleus or CN VII anywhere along its course
• Contralateral paralysis of lower muscles of facial expression	• Ipsilateral paralysis of upper and lower muscles of facial expression
• Forehead is spared due to its bilateral UMN innervation	• Causes: - Bell palsy (idiopathic—most common) - Lyme disease, herpes simplex, herpes zoster (Ramsay Hunt syndrome), tumors (e.g., parotid gland)



FACIAL NERVE LESIONS (UMNL and LMNL)

Neurocutaneous Disorders

Sturge-Weber syndrome (encephalotrigeminal angiomatosis)	**Mnemonic: STURGE-Weber:** • Sporadic, Port-wine Stain (birthmark) • Tram track calcifications (opposing gyri) • Unilateral; • Retardation (intellectual disability) • Glaucoma (Inc. IOP), GNAQ gene mutation • Epilepsy.	

Tuberous sclerosis	• TSC1/TSC2 mutation on chromosome 16.
	• Autosomal dominant, variable expression.
	• **Mnemonic: HAMARTOMAS:**
	  ◦ Hamartomas in CNS and skin
	  ◦ Angiofibromas
	  ◦ Mitral regurgitation;
	  ◦ Ash-leaf spots
	  ◦ Cardiac Rhabdomyoma (Tuberous sclerosis)
	  ◦ Autosomal dOminant
	  ◦ Mental retardation (intellectual disability)
	  ◦ renal Angiomyolipoma
	  ◦ Seizures, **Shagreen patches** (roughened patches of skin over lumbar spine)
	• ↑ incidence of subependymal giant cell astrocytomas and ungual fibromas	

Neurofibromatosis	**Neurofibromatosis type 1 (von Recklinghausen disease)** • Mutation in NF1 tumor suppressor gene on chromosome 17 which encodes neurofibromin • **Mnemonic:** (17 letters in "von Recklinghausen") • **Café-au-lait spots** • **Cutaneous neurofibromas** • Optic gliomas, • **Pheochromocytomas** • Lisch nodules (pigmented iris hamartomas)	**Neurofibromatosis type 2** • Mutation in NF2 tumor suppressor gene on chromosome 22. **Mnemonic:** NF2 affects 2 ears, 2 eyes, and 2 parts of the brain. • Bilateral acoustic schwannomas • Juvenile cataracts • Meningiomas, and ependymomas.

Neural Tube Defects

- Neuropores fail to fuse (4th week) persistent connection between amniotic cavity and spinal
- canal.
- Associated with maternal diabetes and folate deficiency.
- ↑α-fetoprotein (AFP) in amniotic fluid and maternal serum (except spina bifida occulta = normal AFP).
- ↑ acetylcholinesterase (AChE) in amniotic fluid is a helpful confirmatory test.

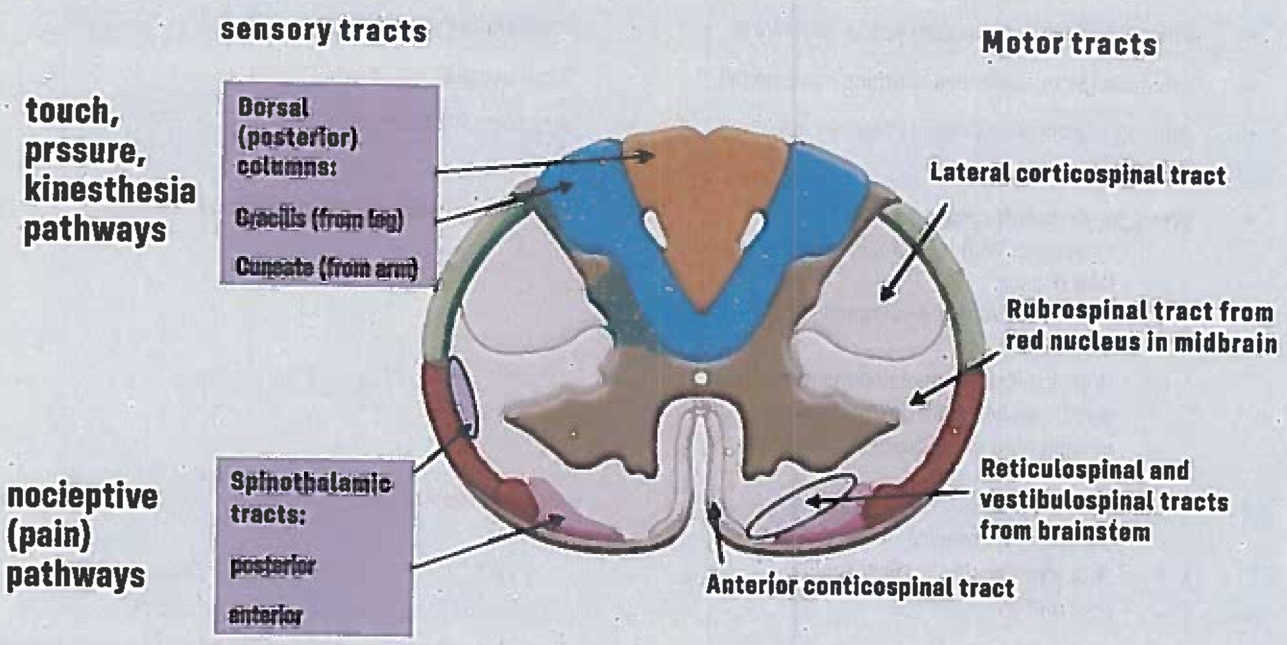
Spina bifida occulta	Failure of caudal neuropore to close, but no herniation
Meningocele	Meninges (but no neural tissue) herniate through bony defect
Myelomeningocele	Meninges and neural tissue (eg, cauda equina) herniate through bony defect
Anencephaly	Failure of rostral neuropore to close → no forebrain, open calvarium. Clinical findings: polyhydramnios (no swallowing center in brain).

Quick Points

Features	Lesion
• Intention tremor	• Cerebellar dysfunction
• Resting tremor (Pill-rolling tremor)	• Substantia nigra (Parkinson disease)
• Chorea (Sudden, jerky, purposeless movements)	• Basal ganglia (Caudate)
• Athetosis (Slow, snake-like, writhing movements)	• Basal ganglia
• Anterograde amnesia (inability to make new memories)	• Hippocampus (bilateral)
• **Wernicke-Korsakoff syndrome** ◦ Mnemonic: Wernicke problems come in a **CAN O'** beer ◦ "Confusion, Ataxia, Nystagmus, Ophthalmoplegia" ◦ Note: In alcoholic or malnourished patients, give thiamine before dextrose to Dec risk of precipitating Wernicke encephalopathy	• Mammillary bodies (bilateral) & medial thalamus
• **Klüver-Bucy syndrome** ◦ Disinhibited behavior ◦ (E.g. Hyperphagia, hypersexuality, hyperorality).	• Amygdala (bilateral)
• Reduced levels of arousal and wakefulness (e.g., coma).	• Reticular activating system (midbrain)
• Parkinsonism+ impairment of vertical gaze	• Progressive supranuclear palsy aka Steele-Richardson-Olszewski syndrome
• Cerebellum lesions features	• Midline Lesions: gait and truncal ataxia • Hemisphere Lesions: intention tremor, past pointing, dysdiadokinesis, nystagmus
• Upbeat nystagmus	• Cerebellar vermis lesions
• Downbeat nystagmus	• Arnold-Chiari malformation (craniomedullary junction pathology)
• **Holmes ADiE syndrome**—usually occurs after zoster infection	• Absent ankle reflexes • Dilated pupil • FEmale gender

Spinal Cord Tracts

Tract	Function	Synapse + Projections	Mnemonic
Ascending Tracts			
Dorsal (Posterior) column tract • Fasciculus cuneatus (upper body, arms) • Fasciculus gracilis (lower body, legs) (remember it as Gracilis muscle in lower legs)	Pressure, vibration, fine touch, proprioception	VPL (thalamus) → sensory cortex	PCT (Posterior Column Tract) does not carry PCT (Pain, Crude touch and Temperature) which are carried by spinothalamic tract
Lateral spinothalamic tract	Pain, Temperature		PaTeLa bone----Pain, Temperature, Lateral spinothalamic tract
Anterior spinothalamic tract	Crude touch, Crude pressure		AC--- Anterior spinothalamic tract Crude touch and Crude pressure
Descending Tract			
Lateral and anterior Corticospinal tract	Voluntary motor	NMJ → muscle fibers	



Spinal Cord Lesions

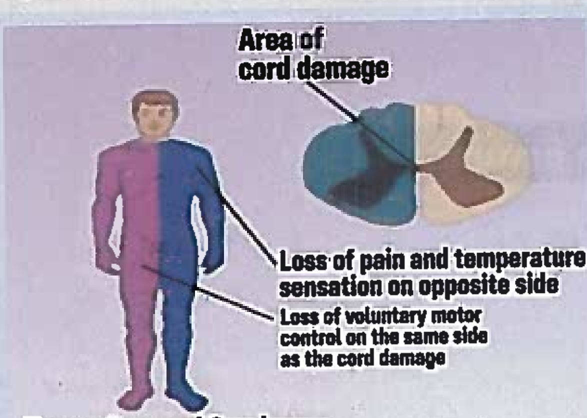
Poliomyelitis	• Caused by poliovirus (fecal-oral transmission). • Replicates in oropharynx and small intestine before spreading via bloodstream to CNS. • Infection causes destruction of cells in anterior horn of spinal cord (LMN death). • Signs of LMN lesion → asymmetric weakness, hypotonia, flaccid paralysis, Fasciculations. • Virus recovered from stool or throat
Tabes dorsalis	• Caused by 3° syphilis. • Results from degeneration (demyelination) of dorsal columns tracts • All posterior (dorsal column) sensations are lost • Urinary bladder is atonic →dribbling of urine • Progressive sensory ataxia (impaired proprioception →poor coordination).

	• Associated with Charcot joints, shooting pain, Argyll Robertson pupils. • Exam will demonstrate absence of Deep Tendon Reflexes s and ⊕ Romberg sign

Vertebral Artery Dissection	• A well-recognized cause of stroke in patients under 45 years
	• Common causes include:
	  ◦ Structural defects of the arterial wall
	  ◦ Connective tissue disease
	  ◦ Trauma (for example, road traffic accident, sporting injury)
	• Features
	  ◦ A young person (average age 40 years) with severe occipital headache and neck pain following a recent head or neck injury

Syringomyelia (Central cord syndrome)	• Development of cavity (syrinx) within the spinal cord
	• If extends into medulla then termed syringobulbia
	• Strongly associated with the Arnold-Chiari malformation, Horner's syndrome
	• Features:
	  ◦ Sensory: spinothalamic sensory loss (pain and temperature)
	  ◦ Motor: wasting and weakness of arms
	  ◦ Loss of reflexes, bilateral upgoing plantars

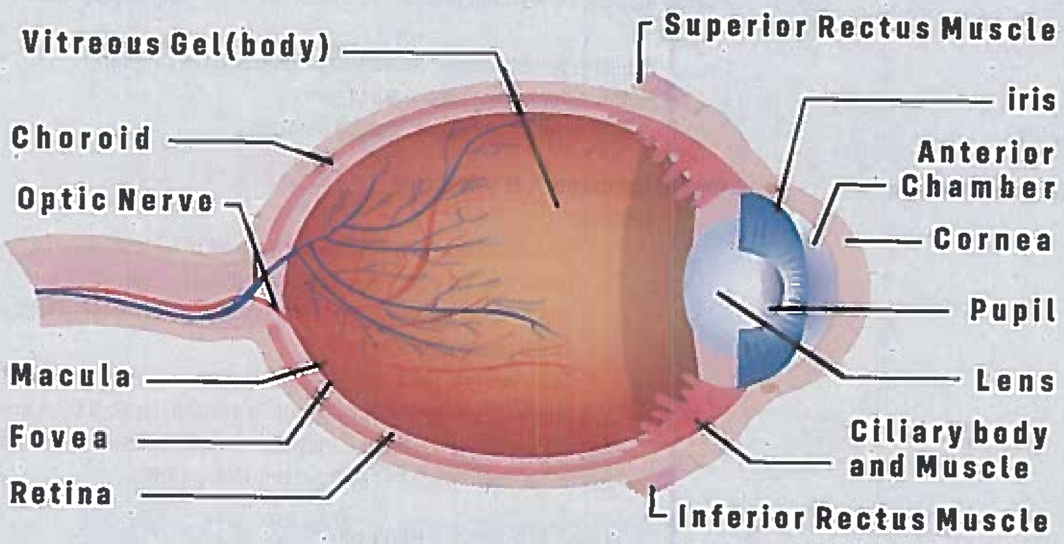
Brown-Séquard syndrome	• **Effect of Hemisection of spinal cord.**
	  ◦ Findings:
	    ▪ Ipsilateral loss of all sensation at level of lesion
	    ▪ Ipsilateral loss of proprioception, vibration, light (2-point discrimination) touch, and tactile sense below level of lesion (due to dorsal column damage).
	    ▪ Contralateral pain, temperature, and crude (non-discriminative) touch below level of lesion (due to spinothalamic tract damage)
	  ◦ If lesion occurs above T1, patient may present with ipsilateral Horner syndrome due to damage of oculosympathetic pathway



Brown Sequard Syndrome

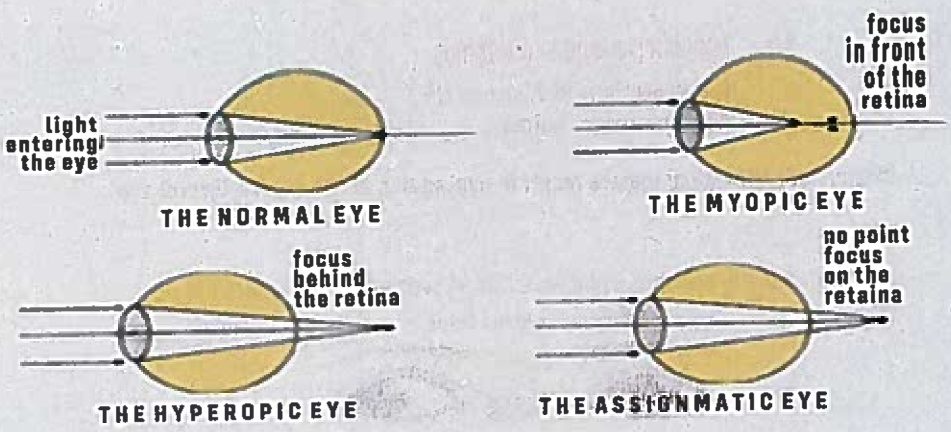
Chapter 3: Special Senses

Normal Eye



Refractive Errors

Error Type	Cause	Correction
Emmetropia	• Normal, Light focuses on the retina.	•
Hypertropia	• Farsighted, Light focuses behind the retina	• Biconvex lens.
Myopia	• Near-sighted, Light focuses in front of the retina	• Biconcave lens
Astigmatism	• Curvature of the lens is not uniform	• Cylindrical lens.
Presbyopia	• Loss of the accommodation power of the lens that occurs with aging • The near point (closest point on which one can focus by accommodation of the lens) moves farther from the eye	• Biconvex lens.



Layers of Retina from Outside In

- Layer of pigment epithelium
- Layer of rods and cones
- External limiting membrane
- Outer nuclear layer
- Outer plexiform layer
- Inner nuclear layer
- Inner plexiform layer
- Ganglion cell layer
- Layer of nerve fibers
- Internal limiting membrane.

Blind spot:

- Rods and cones are not present on the optic disk; the result is a blind spot.

Function of Rods and Cones

Function	Rods	Cones
Sensitivity to light	• Sensitive to low-intensity light; night vision	• Sensitive to high-intensity light; day vision
Acuity	• Lower visual acuity • Not present in fovea	• Higher visual acuity • Present in fovea
Dark adaptation	• Rods adapt later	• Cones adapt first
Color vision	• No	• Yes

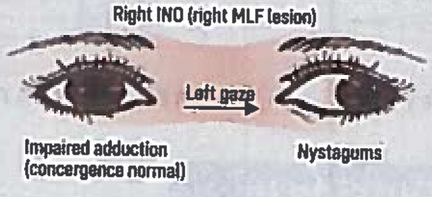
Ophthalmoplegia

Superior colliculus Parinaud Syndrome	Internuclear Ophthalmoplegia (INO)	
• Paralysis of conjugate Vertical gaze (upward gaze)	• Lesion in medial longitudinal fasciculus → A conjugate horizontal gaze palsy • Seen in multiple sclerosis • Internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy. Lack of communication such that when CN VI nucleus activates ipsilateral lateral rectus, contralateral CN III nucleus does not stimulate medial rectus to contract.	NOTE: • **Superior colliculi—conjugate vertical gaze center.** • **Inferior colliculi—auditory.** MNEMONIC: **Your eyes are above** (superior colliculus (visual) **your ears** (inferior colliculus (auditory)

- Abducting eye gets nystagmus (CN VI overfires to stimulate CN III). Convergence normal.

Inernuclear ophtalmoplegiara result in nystagmus of the contra-lateral eye

e.g right INO = nystagmus of left eye (CN VI overfires to stimulate CM III)



Ocular Motility

Nerve supply

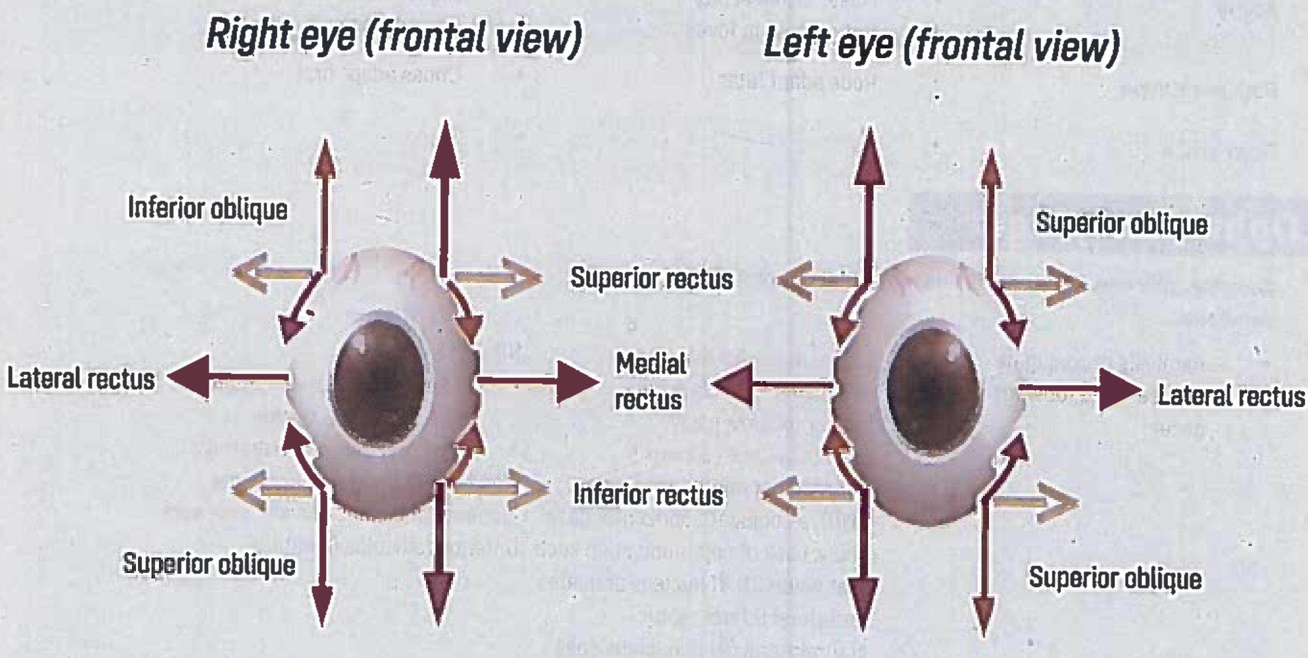
- Mnemonic: **LR6-SO4 Rest 3**
  - **L**ateral **R**ectus→ **6Th** (abducent) cranial nerve
  - **S**uperior **O**blique **4Th** (trochlear) cranial nerve
  - **Rest** all are supplied by → **3RD** (occulomotor) nerve

Action

- Mnemonic: Obliques go Opposite (IO upward, SO downward).

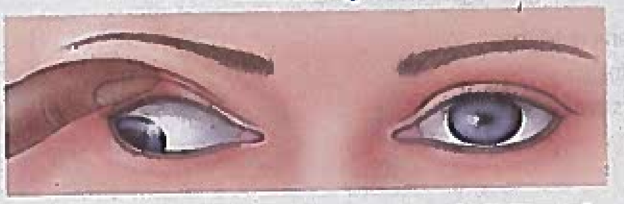
Superior Rectus	Inferior Rectus	Medial Rectus	Lateral Rectus	Superior Oblique	Inferior Oblique
Upward rotation Medial rotation Intortion	Downward rotation Medial rotation Extortion	Medial rotation	Lateral rotation	Downward rotation Lateral rotation Intortion	Upward rotation Lateral rotation Extortion

- Levator palpebrae superioris (muscle of eyelid):
  - Elevation of upper eyelid



Cranial Nerve Palsies

CN III damage

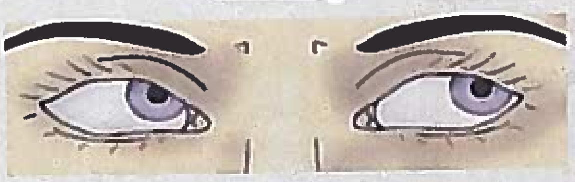


Right eye: Downward and outward gaze, dilated pupil, eyelid manually elevated due to ptosis

Left: Normal

- CN III has both motor and parasympathetic (peripheral) components.
- Motor output:
  - Motor output is to Extraocular muscles
  - Lesion results in ptosis, "down and out" gaze.
- Parasympathetic output:
  - Lesion results in absent pupillary light reflex, "blown pupil" often with "down-and-out" gaze

CN IV damage



- Eye moves upward, particularly with contralateral gaze (problems going down stairs, may present with compensatory head tilt in the opposite direction).

CN VI damage

- Medially directed eye that cannot abduct

Pupillary Control & Ptosis

Miosis	• Constriction, parasympathetic:
	• 1st neuron: Edinger-Westphal nucleus to ciliary ganglion via CN III
	• 2nd neuron: short ciliary nerves to sphincter pupillae muscles
	• Causes of Miosis (small pupil)
	  • Congenital
	  • Senile miosis
	  • Horner's syndrome
	  • Argyll-Robertson pupil
	  • Pontine hemorrhage
	  • Drugs causes:
	    • Opiates (morphin)
	    • Organophosphate toxicity
	    • Parasympathomimetics: pilocarpine

Mydriasis	• Dilation, sympathetic
	• 1st neuron: hypothalamus to (C8–T2)
	• 2nd neuron: exit at T1 to superior cervical ganglion (travels along cervical sympathetic chain near lung apex, subclavian vessels)
	• 3rd neuron: plexus along internal carotid, enters orbit as long ciliary nerve to pupillary dilator muscles. Sympathetic fibers also innervate smooth muscle of eyelids (minor retractors) and sweat glands of forehead and face
	• Causes of myDriasis (Dilated pupil):
	  • Congenital
	  • Third nerve III palsy
	  • Holmes-Adie pupil
	  • Phaeochromocytoma
	  • Drug causes of mydriasis

	• Topical mydriatics: tropicamide, atropine • Sympathomimetic drugs: amphetamines, cocaine • Anticholinergic drugs: TCA'S

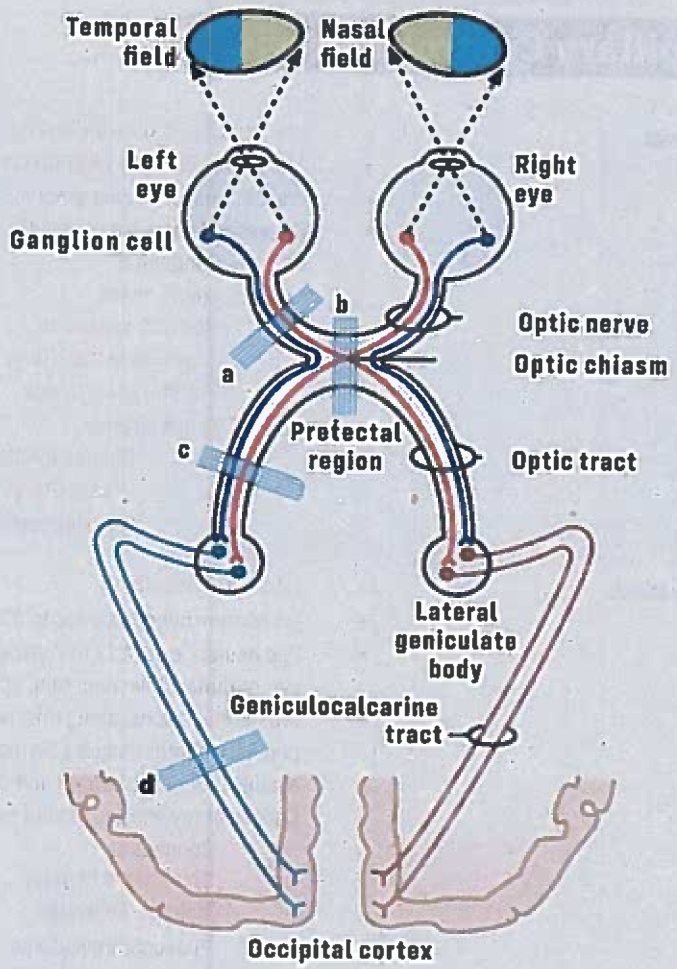
Ptosis	• Ptosis may be unilateral or bilateral
	• <u>Causes of bilateral ptosis:</u>
	  • Myotonic dystrophy
	  • Myasthenia gravis
	  • Syphilis
	  • Congenital
	• <u>Causes of unilateral ptosis: as above plus:</u>
	  • Third nerve palsy
	  • Horner's
	• Important point to remember
	Ptosis + dilated pupil = third nerve palsy
	Ptosis + constricted pupil = Horner's

Horner Syndrome Mnemonic→ **PAM** is **horny** (Horner)	• Sympathetic denervation of face: • Ptosis (slight drooping of eyelid: superior tarsal muscle) • Anhidrosis (absence of sweating) and flushing of affected side of face • Miosis (pupil constriction) • Associated with lesion of spinal cord above T1 (e.g., Brown-Séquard syndrome, late-stage syringomyelia) or Pancoast tumor) , Any interruption results in Horner syndrome

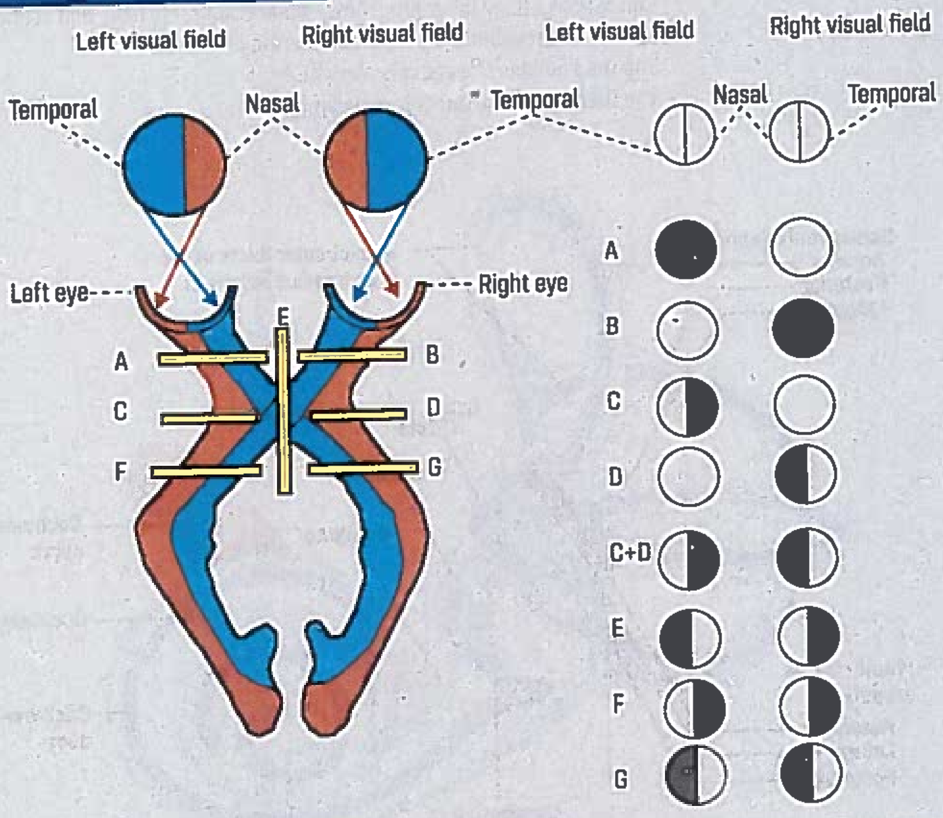
Optic Pathway

Note:

- Lateral geniculate nucleus of thalamus receives visual information from optic tract.
- Medial geniculate nucleus of thalamus receives auditory information



Optic Pathway Lesions



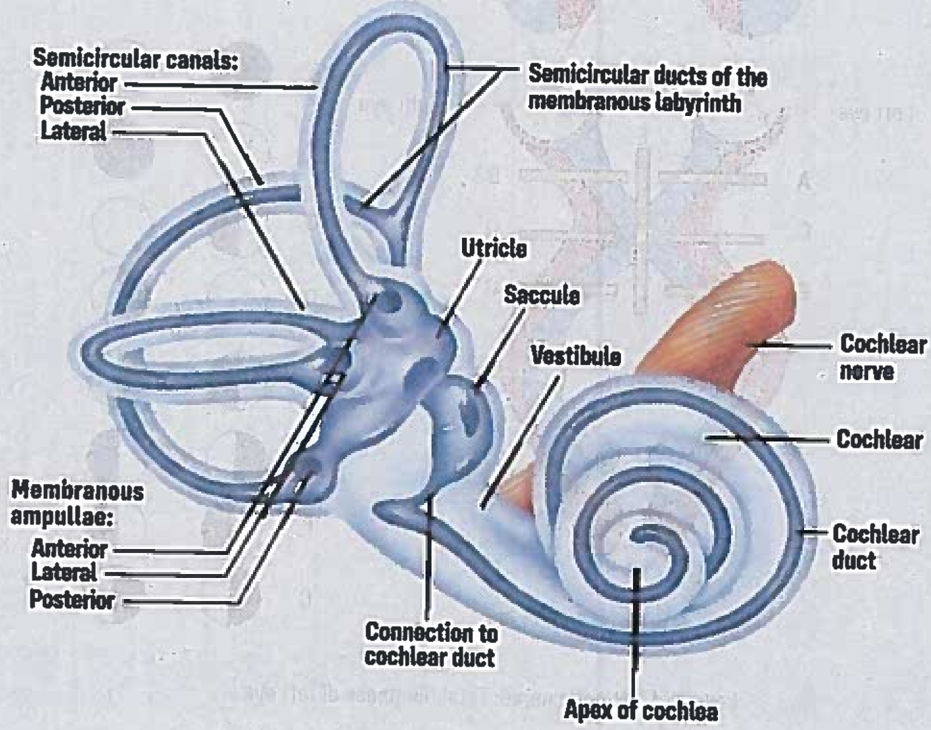
A	Lesion of left optic nerve: Total blindness of left eye
B	Lesion of right optic nerve: Total blindness of right eye
C	Lesion of lateral fibers in left side of optic chiasma: Left nasal hemianopia
D	Lesion of lateral fibers in right side of optic chiasma: Right nasal hemianopia.
C + D	Lesion of lateral fibers in both sides of optic chiasma: Binasal hemianopia
E	Lesion of medial fibers in optic chiasma: Bitemporal hemianopia
F	Lesion of left optic radiation: Right homonymous hemianopia
G	Lesion of right optic radiation: Left homonymous hemianopia
Not shown in fig	Cutting the Geniculocalcarine tract causes homonymous hemianopia with macular sparing

OTOLOGY

Structure of the Ear

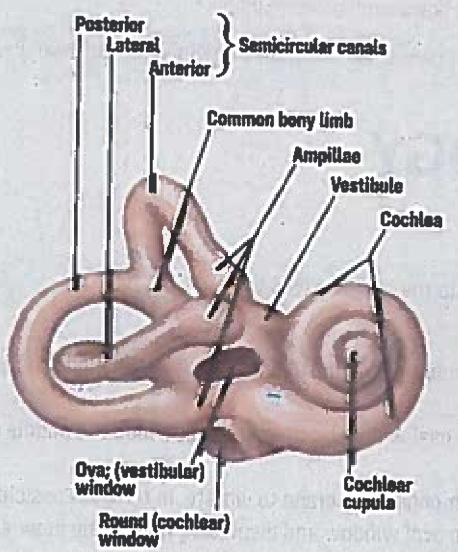
Outer Ear	• Directs the sound waves into the auditory canal
Middle Ear	• Is air filled • Contains the tympanic membrane and the auditory ossicles (malleus, incus, and stapes). • The stapes inserts into the oval window, a membrane between the middle ear and the inner ear. • Sound waves cause the tympanic membrane to vibrate. In turn, the ossicles vibrate, pushing the stapes into the oval window and displacing fluid in the inner ear • Sound is amplified by the lever action of the ossicles and the concentration of sound waves from the large tympanic membrane onto the smaller oval window

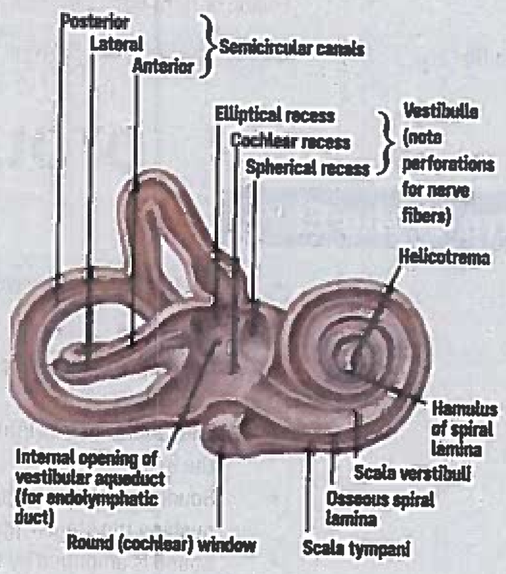
Inner Ear	• Is fluid filled • Consists of a bony labyrinth (semicircular canals, cochlea, and vestibule) and a series of ducts called the membranous labyrinth. • The fluid outside the ducts is perilymph • The fluid inside the ducts is endolymph



Structure of the Cochlea

- Three tubular canals
- The scala vestibuli and scala tympani contain perilymph, which has a high [Na+].
- The scala media contains endolymph, which has a high [K+].
- The scala media is bordered by the basilar membrane, which is the site of the organ of corti.





Vestibular System

- Detects angular and linear acceleration of the head.
- Structure of the vestibular organ:
  - It is a membranous labyrinth consisting of
    - 3 perpendicular semicircular canals, →detect angular acceleration (rotation)
    - Utricle→ linear horizontal acceleration
    - Saccule→linear vertical acceleration

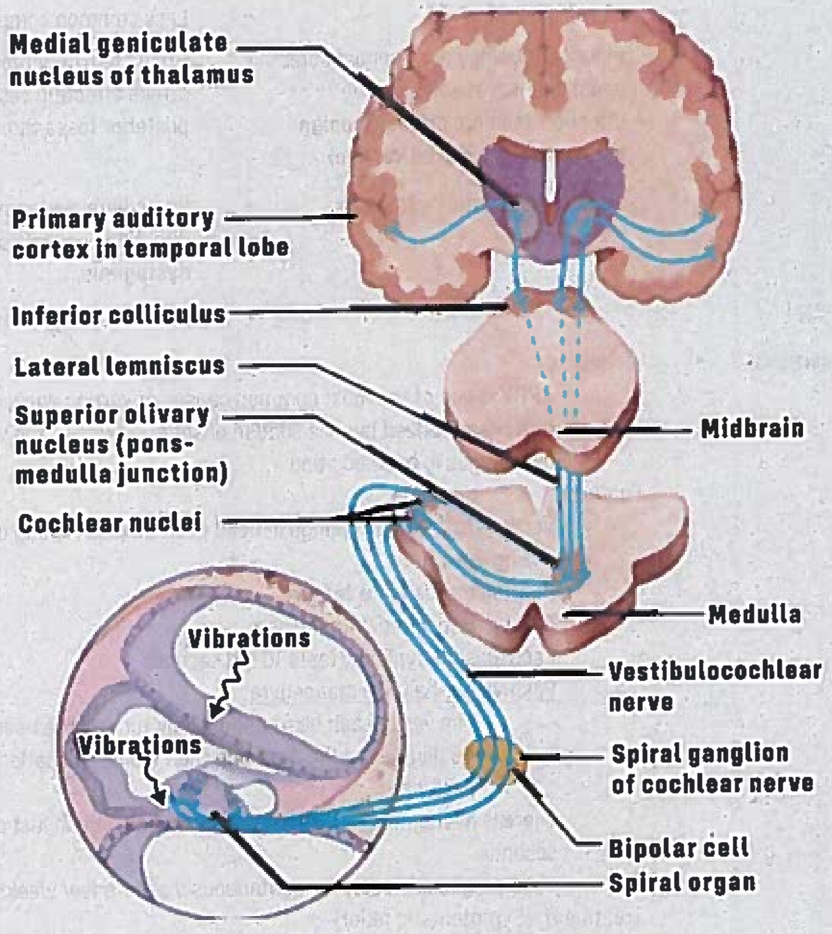
Hearing Loss

- Normally air conduction is twice greater than bone conduction
- Types of hearing loss

	RINNE TEST	WEBER TEST
Conductive	Abnormal (bone > air)	Localizes to affected ear
Sensorineural	Normal (air > bone)	Localizes to unaffected ear

Auditory Pathway

- Fibers ascend through the lateral leminiscus → the inferior colliculus → medial geniculate nucleus of the thalamus → auditory cortex.
- Discrimination of complex features (e.g., recognizing a patterned sequence) is a property of the cerebral cortex



Romberg's Test

Assessment	Romberg's test is a test of the proprioception receptors and pathways function
Romberg's test POSITIVE in	• Positive in conditions causing sensory ataxia such as: ◦ Vitamin deficiencies such as Vitamin B12 ◦ Conditions affecting the dorsal columns of the spinal cord, such as tabes dorsalis (neurosyphilis) ◦ Conditions affecting the sensory nerves (sensory peripheral neuropathies), such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). ◦ Friedreich's ataxia ◦ Ménière's disease ◦ Lumbar spinal stenosis (90%)
Remember Romberg's test is not for the following	• Romberg's test is not a test of cerebellar function. • Patients with cerebellar ataxia will be unable to balance even with the eyes open.

Disease of Ear

Vertigo

- Vertigo Sensation of spinning while actually stationary. Subtype of "dizziness," but distinct from "lightheadedness."
- Types:

Peripheral Vertigo	Central Vertigo
• More common.	• Less common comparatively
• Inner ear etiology (e.g., semicircular canal debris, vestibular nerve infection, Ménière disease, **benign paroxysmal positional vertigo)**	• Brain stem or cerebellar lesion (e.g., stroke affecting vestibular nuclei or posterior fossa tumor).
• Delayed horizontal nystagmus.	• Immediate nystagmus in any direction or **purely vertical nystagmus**
	• Focal neurologic findings.

Benign Paroxysmal Positional Vertigo (BPPV)

- Definition
  - BPPV is one of the most common causes of vertigo encountered.
  - It is characterized by: The sudden onset of dizziness and vertigo, Triggered by changes in head position
- Features
  - Vertigo triggered by change in head position (e.g. Rolling over in bed or gazing upwards)
  - **Hearing loss is not a feature.**
  - May be associated with nausea
  - Each episode typically lasts 10-20 seconds
  - <u>Positive dix-hallpike manoeuvre:</u>
    - The vertigo can be reproduced by turning the head of the patient 45 degrees to the right and then taking the patient to the supine position.
  - There is nystagmus (upbeating and torsional), which last only a few seconds.
  - Good prognosis, resolves spontaneously after a few weeks to months
- Treatment: (Symptomatic relief)
  - Epley manoeuvre (successful in around 80% of cases)
  - Teaching the patient exercises they can do themselves at home, for example Brandt-Daroff exercises
  - Medication –e.g. Betahistine

Meniere's disease	• Definition • A disorder of the inner ear of unknown cause. • Characterized by excessive pressure and progressive dilation of the endolymphatic system. • Features • Episodic vertigo, tinnitus, hearing loss (Sensorineural) • Positive Romberg test • Treatment • Acute attacks: prochlorperazine (dopamine (D2) receptor antagonist—antipsychotic with antiemetic of nausea and vertigo properties, also used in migraine • Prevention: Betahistine may be of benefit
Acoustic neuromas (aka vestibular schwannomas)	• Account for 5% of intracranial tumors and 90% of cerebellopontine angle • Features Features can be predicted by the affected cranial nerves: 5, 7 & 8 cranial nerve V: → absent corneal reflex cranial nerve VII: → facial palsy cranial nerve VIII: → hearing loss, vertigo, tinnitus Bilateral acoustic neuromas are seen in neurofibromatosis type 2 • Investigation MRI of the cerebellopontine angle (investigation of choice)

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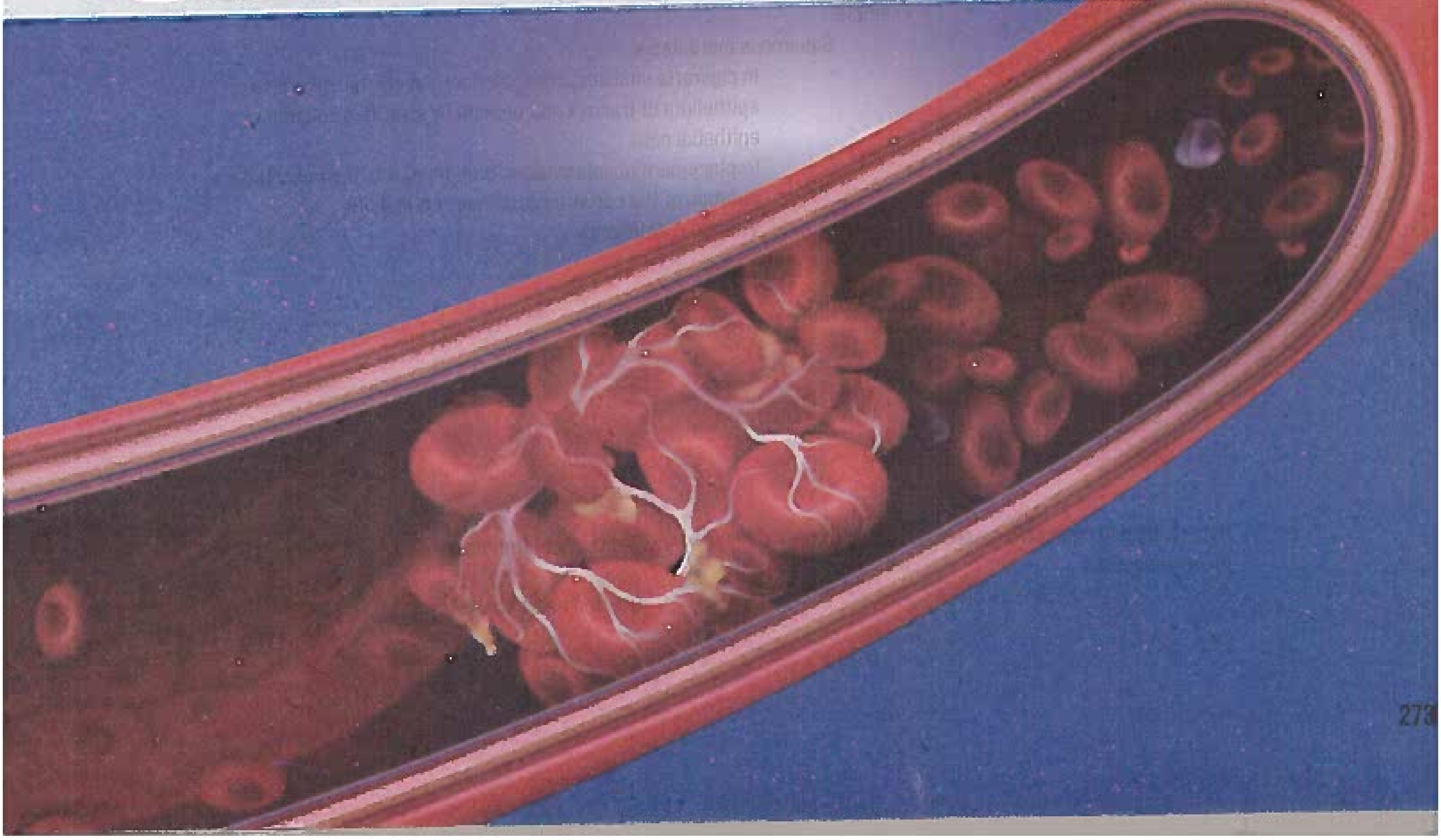
GENERAL PATHOLOGY



Chapter 1:
Cellular Reaction to Injury

Cell Response to Stress

Feature	Explanation

Hypertrophy	• Increase in size of cell resulting in → ↑ in size of organ
	• Example:
	  ◦ Physiological: ↑ muscle mass in exercise
	  ◦ Pathological: ↑ ventricle size in hypertensive heart disease

Hyperplasia	• Increase in number of cells resulting in → ↑ in size of organ
	• Example:
	  ◦ Glandular proliferation of breast during pregnancy
	• Hyperplasia and hypertrophy can occur together.
	• Example:
	  ◦ Enlargement of uterus during pregnancy

Atrophy	• Shrinkage in size of cell as a result of loss of cell substance • Example: ◦ Loss of innervation, diminished blood supply, inadequate nutrition, aging • Atrophy is due to decreased protein synthesis and increase protein degradation through ubiquitin-proteasome pathway, or it can also occur through autophagy (self-eating)

Metaplasia	• Reversible change in which one cell type is replaced by another cell type.
	• Example:
	  ◦ Squamous metaplasia:
	    ▪ In cigarette smokers, change of normal ciliated columnar epithelium of trachea and bronchi by stratified squamous epithelial cells
	    ▪ Replacement of columnar epithelium at the Squamocolumnar junction of the cervix by squamous epithelium
	    ▪ Vitamin A deficiency

Types of Calcification

Metastatic Calcification	Dystrophic Calcification
• Occurs in previously healthy tissues	• Occurs in previously/already damaged tissues
• The cause of metastatic calcification is hypercalcemia	• The cause is not hypercalcemia; typically, the serum calcium concentration is normal.

• Hypercalcemia most often results from any of the following causes:
  ◦ Hyperparathyroidism
  ◦ Osteolytic tumors with resultant mobilization of calcium and phosphorus
  ◦ Hypervitaminosis D
	• Areas of old trauma
	• Tuberculosis lesions
	• Scarred heart valves, and
	• Atherosclerotic lesions

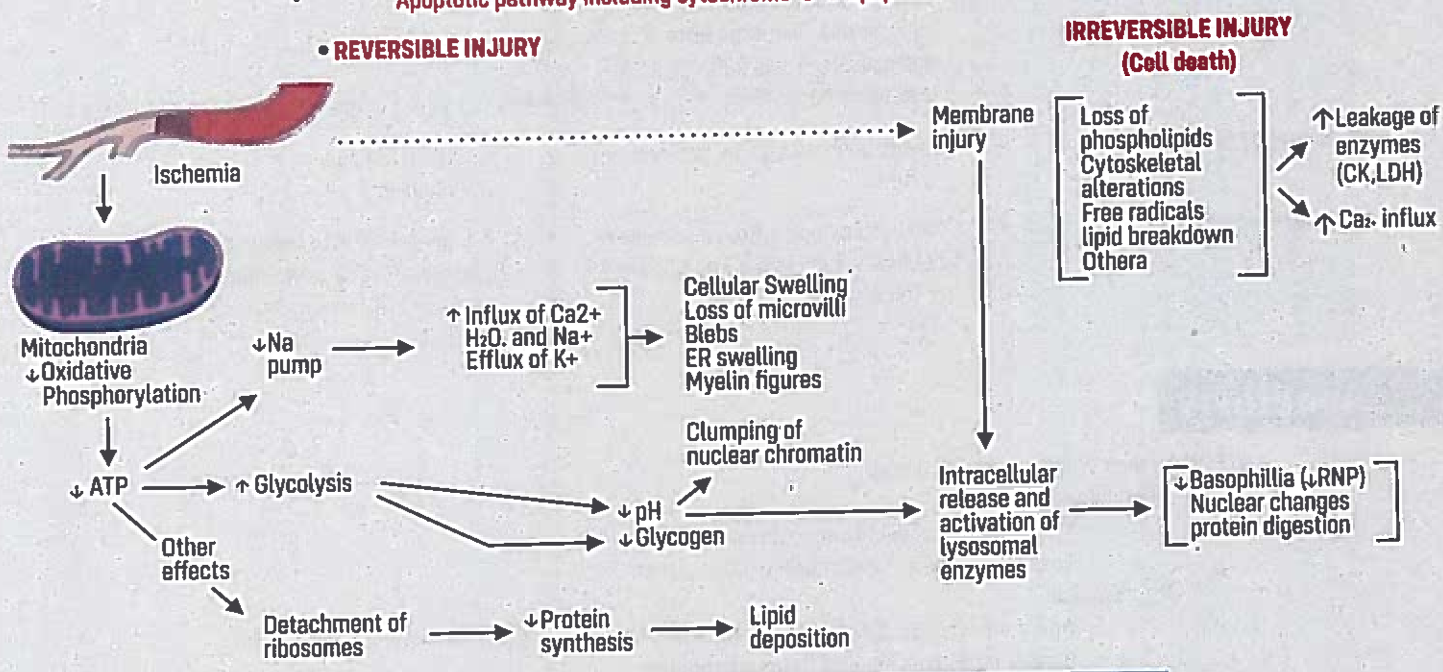
- Excess calcium intake, such as in the milk-alkali syndrome (nephrocalcinosis and Renal stones caused by milk and antacid self-therapy)

Cell Injury and Cell Death

- Causes:
  - Hypoxiareduce oxygen supply to tissue e.g due to anemia, ischemia, cardiorespiratory failure
  - Microorganism
  - Chemicals
  - Aging

Example of Mechanism of Cell Injury

- **Reversible Cell Injury**
  - Ischemia ↓ oxidative phosphorylation in mitochondria → ↓ ATP production, which has the following effects as shown in fig
  - Failure of Na-k pump, as a result Na+ remains inside the cell, Ca+ entry also occurs into cell → resulting in iso-osmotic gain of water causing cell swelling
- **Irreversible Cell Injury and cell death**
  - The hallmark of irreversible injury is membrane damage
  - If ischemia/hypoxia persists beyond reversible cell injury, irreversible cell injury occurs, characterized by following
  - As in reversible cell injury shown in fig →↓pH occurs, as a result lysosomal membrane is damaged and lysosomal enzymes are released causing protein digestion and nuclear changes (Pyknosis, karyolysis)
  - Also injury to plasma membrane occurs due to ↑Ca2+ inside cell, causing activation of phospholipases.
  - Injury to mitochondria as a result of ↑Ca2+ inside, reactive oxygen species etc. will result in
    - ↑Mitochondrial permeability → ↓ATP production Necrosis
    - Apoptotic pathway including cytochrome-C →Apoptosis



Vulnerability of Cells to Irreversible Hypoxic Injury

Feature	Explanation
Neurons	3 to 5 minutes. Purkinje cells hippocampus neurons are more vulnerable to hypoxic injury ("vulnerable hippos").

Myocardial cells and Hepatocytes	One to 2 hours
Skeletal muscle cells	Many hours

Note:

- **Signs of reversible cell injury** → Cellular swelling, ER swelling, Disaggregation of ribosomes leads to failure of protein synthesis, Myelin figures, and Cell blebs.
- **Signs of irreversible injury** → karyolysis, Pyknosis, necrosis, apoptosis

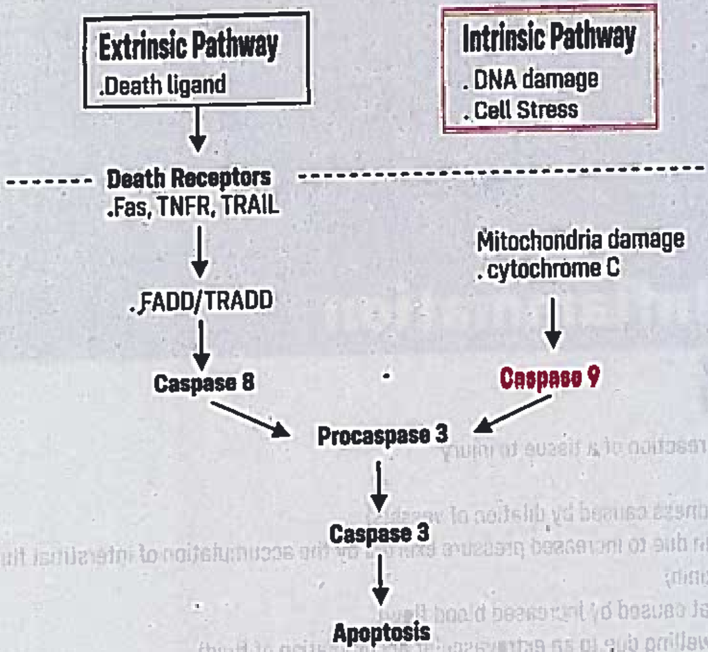
Necrosis

- Enzymatic degradation and protein denaturation of cell due to exogenous injury leading to cell death

Type	Features	Examples
Coagulative	• Basic outline is preserved, but nuclei disappear • Denaturation of proteins	• Ischemia/ infarcts in most tissues e.g., heart (MI), kidney, adrenal gland (except brain)
Liquificative necrosis	• Basic outline is loss. • Enzymatic degradation of proteins	• Brain infarcts • Abscesses
Caseous necrosis	• Architecture not preserved but tissue not liquefied: • Fragmented cells and debris surrounded by lymphocytes and macrophages	• TB • Systemic fungi
Enzymatic fat necrosis	• Pancreatitis → Damaged cells release lipase to break down triglycerides, liberating fatty acids to bind calcium → saponification (Ca+ soap formation)	• Acute pancreatitis
Traumatic fat necrosis	• Severe injury to high fat content tissues	• Breast tissue injury • Abdomen injury
Gangrenous necrosis	• Most often results from interruption of blood supply to a lower extremity or the bowel	• Dry gangrene → Coagulative • Wet gangrene → superinfection, Liquefactive superimposed on coagulative

Apoptosis

- ATP-dependent programmed cell death.
  - Physiological
    - The formation of digits during embryogenesis
    - Loss of endometrial cells during menstruation
  - Physiological
    - Apoptotic removal of cells with irreparable DNA damage (from free radicals, viruses etc.), protecting against neoplastic transformation



Intrinsic (Mitochondrial Pathway)	Extrinsic (Death Receptor) Pathway
• Regulated by Bcl-2 family of proteins. • BAX and BAK are proapoptotic, • While Bcl-2 and Bcl-x are antiapoptotic.	• Initiated by Fas or TNF-α binding to its receptor
• Intrinsic pathway activates caspases 9	• Extrinsic pathway activates caspases 8

Chapter 2: Inflammation

Inflammation

- Inflammation is a reaction of a tissue to injury
- Cardinal signs
  (1) Rubor (redness caused by dilation of vessels)
  (2) Dolor (pain due to increased pressure exerted by the accumulation of interstitial fluid and to mediators such as bradykinin)
  (3) Calor (heat caused by increased blood flow)
  (4) Tumor (swelling due to an extravascular accumulation of fluid)
  (5) Functio laesa (loss of function)

Acute Inflammation

- Acute inflammation is rapid onset (seconds to minutes) and of short duration (minutes to days).
- **Components of Acute Inflammation**
  - **Vascular changes**
  - Initial vasoconstriction for few seconds, followed by vasodilation
  - ↑ vascular permeability, leading to leakage of proteins (edema)
  - **Cellular changes**

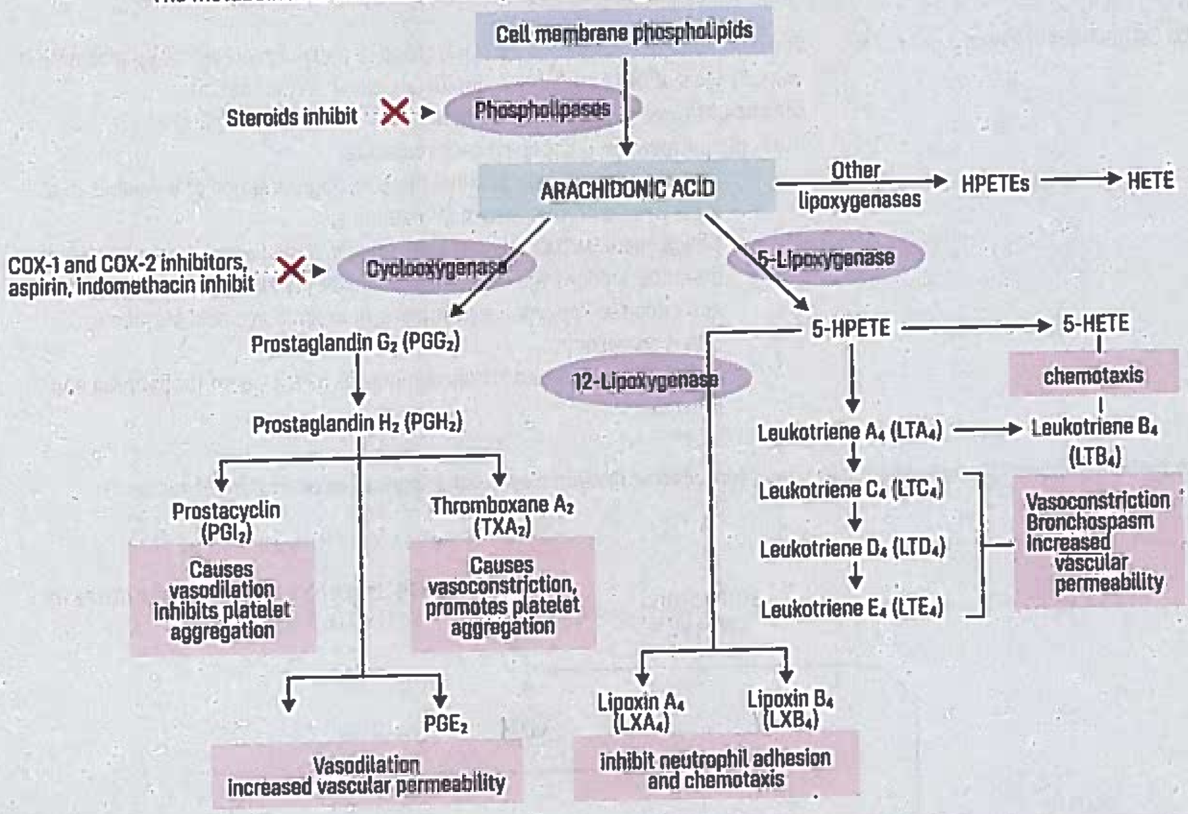
Step-1 → Margination	• Vasodilation slows blood flow in postcapillary venules. • As a result RBC's acquire central position while leucocytes (neutrophils) get peripheral/marginal position.
Step-2 → Rolling	• Leukocytes stick to endothelium and roll along its surface • Mediated by the action of endothelial selectins
Step-3 → Adhesion	• Leukocytes adhere to the endothelial surface • Mediated by the interaction of integrins on leukocytes • Cellular adhesion molecules (are ICAM and VCAM) are upregulated on endothelium by TNF and IL-1
Step-4 → Transmigration and	• Leukocytes transmigrate across the endothelium of postcapillary venules and move toward chemical attractants (chemotaxis).
Step- 5 → Phagocytosis	• Neutrophils and monocytes-macrophages are the most important phagocytic cells. • Recognition and attachment → via Opsonins (C3b and IgG) • Engulfment • Killing and degradation **Oxygen dependent killing** • Phagocytosis stimulate NADPH • Oxidation of NADPH produces superoxide ion (O2-) • O2- is converted into Hydrogen peroxide H2O2 • H2O2 and Cl- are converted to Hyochlorite (HOCL) by MPO. • H2O2 oxidizes microbial proteins and disrupts cell walls **Non-Oxygen dependent killing** • Less effective than oxygen-dependent microbial killing. • Mediated by • Lysozyme, • Lactoferrin, • Major basic protein of eosinophils, • Defensins.

Mediators of Acute Inflammation

- Divide into Cell derived and Plasma derived mediators
- For details see fig in summary of mediators of acute inflammation given after few pages

Cell Derived Mediators

- Histamine → causes vasodilation, released from mast cells, basophils, and platelets
- Serotonin → causes vasodilation, released from platelets.
- Cytokines → major cytokines are IL-1, TNF, they causes fever, Neutrophilia and shock.
- Arachidonic acid metabolites (prostaglandins, leukotrienes etc.)
  - Phospholipase A2 stimulates the release of Arachidonic acid from membrane phospholipids.
  - The metabolism of Arachidonic acid proceeds along two pathways:



The Cyclooxygenase Pathway

- Catalyzed by two enzymic isoforms, referred to as cyclooxygenase-1 and cyclooxygenase-2 (COX-2).
- This pathway is inhibited by aspirin and other anti-inflammatory drugs
- It yields thromboxanes and prostaglandins
- Thromboxane A2 (TxA2) in platelets, prostacyclin (PGI2) in endothelial cells, and other prostaglandins in other tissues.
- Platelet TxA2 is a powerful vasoconstrictor and platelet aggregant.
- Endothelial PGI2 is a powerful vasodilator and inhibitor of platelet aggregation.

The Lipoxygenase Pathway

- It yields hydroperoxyeicosatetraenoic acid (HPETE) and its derivatives, 12-HPETE and 5-HPETE.
- 5-HPETE in turn gives rise to 5-HETE, a chemotactic factor for neutrophils.
- 5-HPETE also gives rise to leukotrienes:
  - LTB4, a chemotactic factor for neutrophils
  - LTC4 which is converted into LTD4, and LTE4, are potent vasoconstrictors, bronchoconstrictors, and mediators of increased capillary permeability, which are sometimes jointly referred to as the slow-reacting substance of anaphylaxis
- 5-HPETE also indirectly gives rise to lipoxins (LX). LXA4 and LXB4

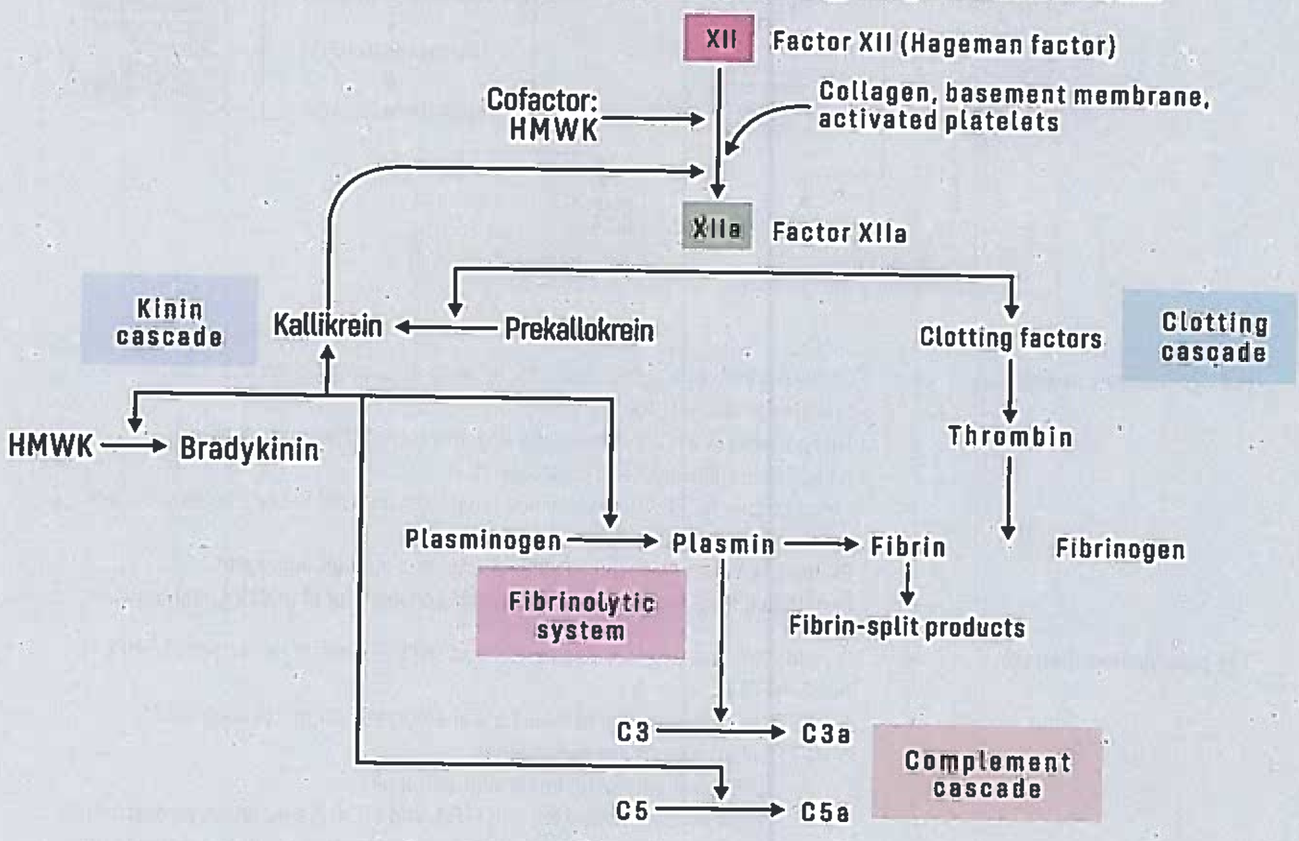
Plasma Derived Mediators

- 2 system, kinin system and complement system

The kinin system	• Is initiated by activated Hageman factor (factor XIIa).
	• Factor XIIa also activates the intrinsic pathway of coagulation and the plasminogen (Fibrinolytic) system
	• Activation of this system in turn activates the complement cascade. Thus, factor XIIa links the kinin, coagulation, plasminogen, and complement systems.
	  • This system converts prekallikrein to kallikrein (a chemotactic factor).
	  • It results in the cleavage, by kallikrein, of high-molecular-weight kininogen to bradykinin that mediates vascular permeability, arteriolar dilation, and pain.

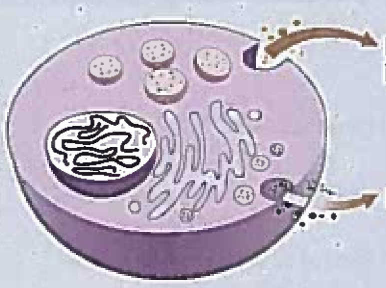
The Complement system.	• The complement system consists of a group of plasma proteins that participate in immune lysis of cells and play a significant role in inflammation.
	• **Classic** pathway→ IgG or Ig**M** mediated (**GM** makes **Classic** cars)
	• Alternate pathway→ microbe surface molecule
	  • C3a and C5a (anaphylatoxins) mediate degranulation of basophils and mast cells with the release of histamine.
	  • C5a is chemotactic, mediates the release of histamine from platelet-dense granules, induces the expression of leukocyte adhesion molecules, and activates the lipoxygenase pathway of arachidonic acid metabolism.
	  • C3b is an opsonin.
	  • C5b-9, the membrane attack complex, is a lytic agent for bacteria and other cells.

The fig below shows interrelationship between four plasma mediator systems triggered by activation of factor XIIa



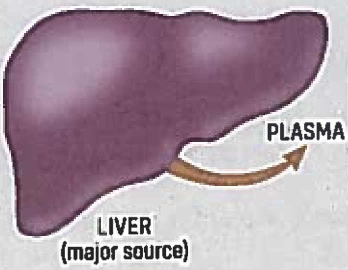
Summary of Mediators of Acute Inflammation

CELL-DERIVED



	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophills, platelets
	Serotonin	Platelets
Newly synthesized	Prostaglandins	All leukocytes,mast cells
	Leukotrienes	All leukocytes,mast cells
	Platelet-activating factor	All leukocytes,EC
	Reactive oxygen species	All leukocytes
	Nitic oxide	Macrophages, EC
	cytokines	Macrophages, lymphocytes, EC, mast cells
	Neuropeptides	Leukocytes, nerve fibers

PLASMA PROTEIN-DERIVED



- Complement Activation
  - C3a, C5a – anaphylatoxins
  - C3b
  - C5b-9 (membrane attack complex)
- Factor XII (Hageman factor) activation
  - Kinin system (bradydinin)
  - Coagulation / fibrinolysis system

Vasoconstriction	• TxA_2 (stimulates platelet aggregation) • LTC_4, LTD_4, LTE_4 • PAF
Vasodilation	• PGI_2 (Inhibitor of platelet aggregation) • PGD_2, PGE2, $PGF_2\alpha$ • Bradykinin • PAF • Nitric oxide
Anaphylaxis	• C3a, C4a, C5a
Neutrophils chemotaxis	• C5a, LTB_4, IL-8
Opsonins	• C3b and IgG (C3b binds bacteria)
Cytolysis	• C5b-9 causes cytolysis by membrane attack complex

Types of Inflammatory Cells

Cell Type	Features
Neutrophils	• Most prominent cells in acute inflammation if first 24 hours, and disappears within 24-48 hours • Causes include Bacterial infections and Any acute inflammation e.g. infarction
Monocytes-macrophages	• After 1-2 days, neutrophils are replaced by monocyte-macrophages • Also involved in chronic inflammation • Causes of monocytosis include any chronic infection (TB, malignancy)
Lymphocytes	• Prominent inflammatory cells in many viral infections
Eosinophils	• Inflammatory cells in allergic reactions and parasitic infestations
Mast cells and basophils	• Both are sources of histamine. • Important causes of basophilia include chronic myelogenous leukemia and other myeloproliferative diseases.

Hereditary Defects That Impair the Acute Inflammatory Response (Defects in Leucocytes)

Disease	Characteristics
Chronic granulomatous disease of childhood	• X-linked disorder, NADPH oxidase defect • In this disease organism is ingested but few organism cannot be killed • Catalase-positive organisms ◦ Catalase-positive organisms are ingested but not killed.(e.g. Staphylococcus aureus) ◦ These organisms can destroy H_2O_2 generated by bacterial metabolism. ◦ Because enzyme-deficient neutrophils cannot produce H_2O_2 and bacterial H_2O_2 is destroyed by bacterial catalase. ◦ H_2O_2 is not available as a substrate for myeloperoxidase. ◦ Thus, the myeloperoxidase–halide system of bacterial killing fails. • Catalase-negative organisms ◦ Catalase-negative organisms are ingested and killed (e.g. streptococci) ◦ These organisms produce sufficient H_2O_2 to permit oxygen-dependent microbicidal mechanisms to proceed. ◦ In effect, the substrate for myeloperoxidase is produced by the bacteria, and the bacteria in a sense kill themselves.
Chédiak-Higashi syndrome	• Impaired chemotaxis and migration characterized by ◦ Increased risk of pyogenic infections ◦ Neutropenia (due to intramedullary death of neutrophils) ◦ Giant granules in leukocytes (due to fusion of granules arising from the ◦ Golgi apparatus) ◦ Albinism ◦ Peripheral neuropathy
Leukocyte adhesion deficiency (LAD)	• LAD type-1: ◦ Associated with recurrent bacterial infections ◦ Results from the deficiency of β2-integrins. • LAD type-2: ◦ Also associated with recurrent bacterial infections ◦ Results from mutations in the gene that codes for fucosyltransferase, required for the synthesis of sialyl-Lewis X on neutrophils.

Granulomatous Inflammation (Chronic Inflammation)

- Granulomas are composed of epithelioid cells (macrophages with abundant pink cytoplasm) with surrounding multinucleated giant cells and lymphocytes
- Causative agents:
  - Bacterial
    - Mycobacterium tuberculosis and M. leprae
    - Treponema pallidum (tertiary syphilis)
    - The bacterium of cat-scratch disease (Bartonella henselae)
  - Fungal → Endemic mycoses (e.g., histoplasmosis)
  - Parasitic → Schistosomiasis
  - Foreign body
  - Auto inflammatory:
    - Sarcoidosis (Diagnosis of sarcoidosis requires non-caseating granulomas on biopsy)
  - Crohn disease and Granulomatosis with polyangiitis (Wegener) etc.

Chapter 3: Hemodynamic Dysfunction

Hyperemia

- Hyperemia (congestion) represents the increase of blood in a territory, due to dilatation of small vessels. According to the mechanism, it may be active or passive.
- Active hyperemia (congestion) is a result of arteriolar distension (e.g., skeletal muscle activity, inflammation, local neuro-vegetative reaction).
- Passive hyperemia (congestion), also termed stasis, is a consequence of an impaired venous drainage (heart failure,
- compression or obstruction of veins), followed by dilatation of venules and capillaries.

Types of Infarcts

Red infarcts / hemorrhagic infarcts	Yellow infarcts / anemic infarcts
Red (hemorrhagic) infarcts occurs in tissues with multiple blood supplies	Pale (anemic) infarcts occur in solid organs with a single (end-arterial) blood supply.
Example → Liver, Lung, Intestine, testes, reperfusion (e.g., after angioplasty).	Examples → Heart, Kidney, and Spleen.
Reperfusion injury is due to damage by free radicals. (Red=Reperfusion=Radicals)	

Shock

- Inadequate organ perfusion and delivery of nutrients necessary for normal tissue and cellular function.

Type / Features	Hypovolemic	Cardiogenic	Obstructive	Septic shock
Caused By	Hemorrhage dehydration burns	Acute MI, HF. valvular dysfunction, arrhythmia	Cardiac tamponade, pulmonary embolism tension pneumothorax	Sepsis
Skin	Cold, clammy	Cold, clammy	Cold, clammy	Warm
PCWP (Preload)	↓↓	Can be ↓ or ↑	Can be ↓ or ↑	↓
Cardiac Output	↓	↓	↓	↑
Heart Rate	↑	↑	↑	↑
Systemic Vascular Resistance (AFTERLOAD)	↑	↑	↑	↓
Oxygen Delivery	↓	↓	↓	↑

Clotting Factors

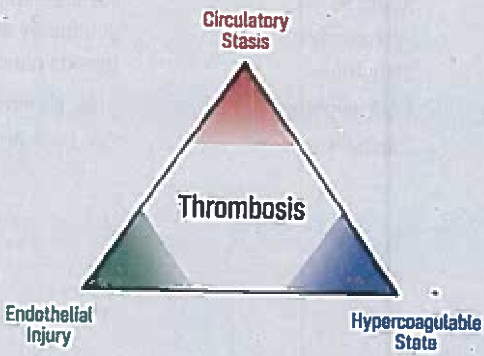
- Fit Pants, Tight Collars, Loose American Shirts Are Cool, "Says Pretty Heroine Farah"!

Clotting Factor	Synonyms
Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue factor
Factor IV	Calcium
Factor V	Labile factor, Proaccelerin,
Factor VI	Un-Assigned
Factor VII	Stable factor
Factor VIII	Antihemophilic factor A
Factor IX	Christmas factor or Antihemophilic factor B or
Factor X	Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor

- Note:
  - All clotting factors are proteins and synthesized in liver except:
    - Factor IV: calcium
    - Factor VIII Carrier Protein (vWF vonWillebrond factor)

Thrombosis

- Thrombosis is intravascular coagulation of blood, often causing significant interruption of blood flow.
- Pathologically predisposition to this condition is by
  - Venous stasis, usually from immobilization, CHF, Polycythemia, sickle cell disease
  - Use of oral contraceptives, especially in association with cigarette smoking.
- Virchow's triad describes the three broad categories of factors that are thought to contribute to thrombosis
  - Hypercoagulability
  - Hemodynamic changes (stasis, turbulence)
  - Endothelial injury/dysfunction



Thrombogenesis

- This process results from the interaction of platelets, damaged endothelial cells, and the coagulation cascade.

1. **Platelets**
   a. **Platelet adhesion** → Vessels injury → endothelial exposure → platelets adhere to it and release ADP, histamine and serotonin → activation of coagulation cascade
   b. **Platelet aggregation** → Platelets stick to each other helped by TxA2, PAF

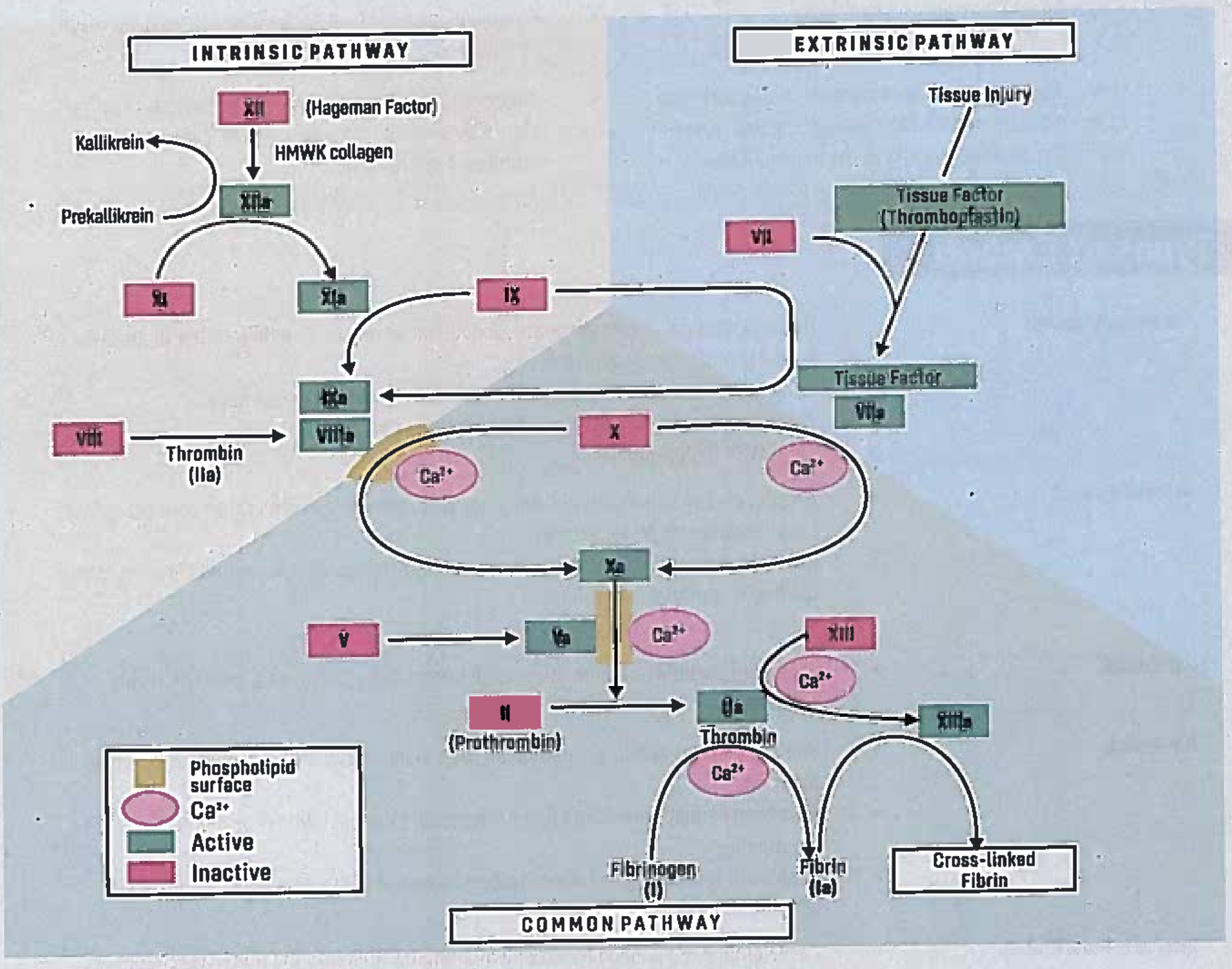
c. Platelet plug is stabilized by fibrinogen

2. **Endothelial cells:**

a. Intact endothelial cells opposes coagulation by synthesizing and releasing PGI2 and NO (which inhibits platelet aggregation) also by taking up, inactivating, and clearing thrombin.

3. **Coagulation Cascade**

Extrinsic Pathway	• Initiated by tissue factor, which activates factor VII and forms a tissue factor-factor VIIa complex • The complex initiates coagulation through the activation of factor X to factor Xa (and additionally factor IX to factor IXa). • Factor Xa converts prothrombin (factor II) to thrombin (factor IIa) • Factor Va is a cofactor required in the conversion of prothrombin to thrombin. • Thrombin converts fibrinogen to fibrin • The prothrombin-mediated cleavage of fibrinogen results in a fibrin monomer, which is polymerized and stabilized by factor XIII, thus forming the fibrin clot.
Intrinsic Pathway	• Involves the activation of all clotting factors with the exception of factors VII and XIII. • When factor XII comes in contact with collagen, it is converted into activated factor XIIa, which in turn converts factor XI to activated XIa • Activated factor IX activates factor Xa in presence of calcium and factor VIII
Common Pathway	• Factor Xa converts prothrombin into thrombin, which forms the fibrin clot



Intrinsic Vs. Extrinsic Pathway

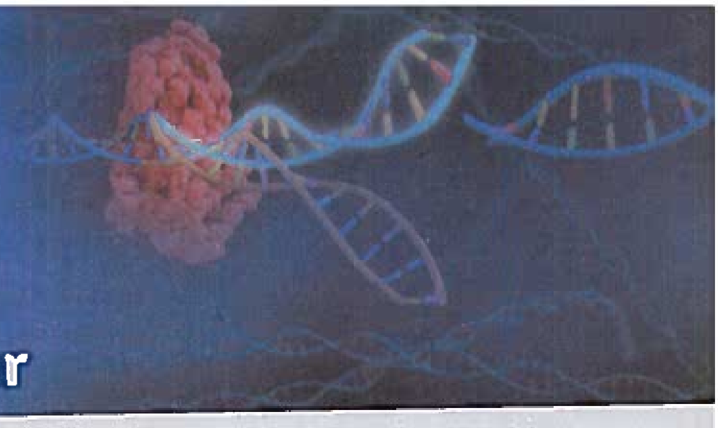
Intrinsic Pathway	Extrinsic Pathway
• Intrinsic pathway is activated by subendothelial collagen.	• Extrinsic pathway is activated by tissue thromboplastin
• aPTT is used to check it, which is a measure of factors II, V, VIII, IX, X, XI, XII, and fibrinogen	• Prothrombin time (PT) is used to check it, which is a measure of factors II, V, VII, X, and fibrinogen.
	• Factors X, IX, VII, and II, protein C and S are Vitamin K dependent factors.
• Heparin acts on intrinsic pathway	• Warfarin acts on extrinsic pathway(inhibit the enzyme Vit-k reductase)
Mnemonic: PT Trainer made us did H**IP** exercises while counting from **8- two- 12**. • **PTT** is used to check **I**ntrinsic **P**athway, factors are **8,9,10,11,12** and **2**	**Mnemonic: WEPT 1972** • **W**arfarin acts on **E**xtrinsic pathway, **PT** is used to check it, factors are **10, 9 ,7, 2**

Types of Thrombi

Arterial thrombi	Venous thrombi
• Formed in areas of active blood flow	• Formed in areas of less active blood flow, most often in the veins of the lower extremities
• When mature, they demonstrate alternate dark gray layers of platelets interspersed with lighter layers of fibrin. This layering results in the lines of Zahn.	• They are dark red with a higher concentration of red cells than arterial thrombi. Lines of Zahn are not prominent or are absent

Types of Emboli

Pulmonary Emboli	• Important cause of sudden death, usually occurring in immobilized postoperative patients and in those with CHF. • Immobilization leads to venous thrombosis in the lower extremities. • Thrombus break away and travel to pulmonary artery. • Treat with hyperbaric O_2
Arterial Emboli	• Arterial emboli usually arise from a mural thrombus (thrombus that adheres to one heart chamber or major artery). • Example: Branches of the carotid artery, most frequently the middle cerebral artery, leading to cerebral infarction
Fat Emboli	• These are particles of bone marrow and other fatty tissue as a result of severe fractures
Air Emboli	• Due to air entering into circulation as seen in penetrating chest injury or criminal abortion. • Also seen in deep-sea divers (decompression sickness) who return to the surface too rapidly. • Bubbles of relatively insoluble nitrogen come out of solution and obstruct the circulation
Amniotic Fluid Emboli	• These emboli are caused by escape of amniotic fluid into the maternal circulation. • They can activate the coagulation process, leading to DIC. • They can cause maternal death



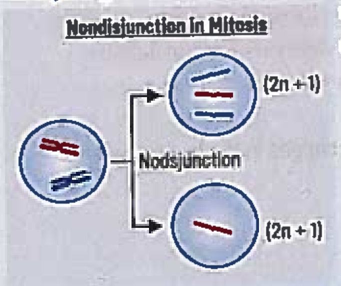
Chapter 4: Genetic Disorder

Chromosomal Disorders

Normal

- Normally cells are diploid, containing 46 chromosomes (multiple of 23)
- Out of which 22 pairs of autosomes
- And 1 pair of sex chromosome i.e. XX in females or XY in males

Aneuploidy



- Haploid number, chromosome number that is not a multiple of 23.
- It is caused most often by an addition or loss of one or two chromosomes.
- This change may result from nondisjunction or anaphase lag.

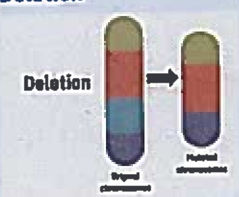
Non-disjunction

Chromosomes fail to separate during mitosis or meiosis (most common)
e.g. trisomy 21 (Down syndrome)

Anaphase lag

Loss of chromosome during mitosis or meiosis

Deletion

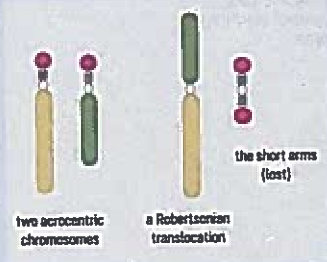


- Absence of a portion/or entire chromosome
- E.g. Change is denoted by a minus sign following the number of the chromosome
- And the sign for the chromosomal arm involved, p for the short arm and q for the long arm.
- For example, cri du chat syndrome, characterized by partial loss of the short arm of chromosome 5, is designated as 46XY, 5p- in males or 46XX, 5p- in females.

Inversion

- Inversion is a reunion of a chromosome broken at two points, in which the internal fragment is reinserted in an inverted position.

Translocation



- This is exchange of chromosomal segments between chromosomes (nonhomologous)
- It is denoted by a "t" followed by the involved chromosomes in numeric order.
- For example, the translocation form of Down syndrome is designated as t (14q; 21q).
- Types

Reciprocal or balanced translocation

- Break in two chromosomes leading to an exchange of chromosomal material
- No genetic information is lost.

Robertsonian translocation

- Translocation caused by breaks at or near the centromeres of two acrocentric chromosomes (chromosomes in which the short arm is very short)
- In this translocation short arms are lost. E.g., Down syndrome

Sex chromosome and Barr Bodies

- Sex chromosomes are XY (in males), XX (females)
- Barr bodies. Also known as sex chromatin, is the inactive X chromosome in a female somatic cell
- The number of Barr bodies is always one less than the number of X chromosomes.
  - Normal female cells (XX) have one Barr body;
  - Normal male cells (XY) have no Barr bodies
  - XXXY cells have two Barr bodies

Abnormalities of Autosomal Chromosomes

1. Down Syndrome

Frequency	• Most common chromosomal disorder.	
Causes	Trisomy 21	Translocation
	About in 95% cases	3% to 5% of cases
	Meiotic non-disjunction is usual cause	Translocation leads to a familial form of Down syndrome, with significant risk of the syndrome in subsequent children
	Incidence increases with maternal age	No relation to maternal age.
Characteristics	• Mental retardation. Large forehead, broad nasal bridge, wide-spaced eyes, epicanthal folds, large protruding tongue, and small low-set ears, simian crease, a single palmar crease, Short, broad hands with curvature of the fifth finger; simian crease, a single palmar crease; and an unusually wide space between the first and second toes	
Complications	• Congenital heart disease, especially defects of the endocardial cushion, including atrioventricular valve malformations and atrial and ventricular septal defects • Acute leukemia (20-fold increase), most often lymphoblastic • Increased susceptibility to infection • In patients surviving into middle age, morphologic changes in the brain similar to those of Alzheimer disease	

Maternal screening for Down syndrome	• Triple screen
	  • B-HCG is increased.
	  • Alpha feto protein is decreased
	  • Estriol is decreased.
	• Quadruple screen
	  • And if we add up inhibin which is increased then it will be called as quadruple test or tetra screen	

Abnormalities of Autosomal Chromosome (Continued)

Cri du chat (5p-, cry of the cat) syndrome	Mnemonic: **SMALL HEAD CAT is CRYING because she lost 5$ in her HEART SHAPED PURSE** • Microcephaly, mental retardation, Cat like cry, deletion of short arm of chromosome 5, congenital heart diseases.
DiGeorge/velocardiofacial syndrome (microdeletion of 22q11, CATCH 22 syndrome)	Mnemonic: **CATCH 22** • Cardiac abnormalities, Abnormal facies, T-cell deficit because of Thymic hypoplasia, Cleft palate, Hypocalcemia because of hypoparathyroidism, and microdeletion 22q11
Edwards syndrome (trisomy 18)	Mnemonic: **PRINCE E**dward • **P**rominent occiput, **R**ocker-bottom feet, **I**ntellectual disability, **N**ondisjunction (most common cause), **C**lenched fists (with overlapping fingers), low-set **E**ars
Patau syndrome (trisomy 13)	Mnemonic: (Trisomy 13= 3M, 3P) • **M**ental retardation, **M**icrocephaly, **M**icrophthalmia • Cleft li**p** and **p**alate, **P**olydactyly

- Note: **D**own syndrome (trisomy **21**) → **D**rinking age is **21**
- **E**dwards syndrome (trisomy **18**) → **E**lection age is **18**
- **P**atau syndrome (trisomy **13**) → **P**uberty age is **13**

Abnormalities of Sex Chromosomes

Klinefelter Syndrome [Male] (47, XXY)

- Klinefelter syndrome occurs when there are at least two X chromosomes and one or more Y chromosomes.
- Karyotype 47, XXY is characteristic
- Variants include additional X chromosomes (e.g., XXXY)
- **Findings:**
  - Manifested by male
  - Male hypogondisam
  - Atrophic testes
  - Gynecomastia
  - Tall stature
  - Dysgenesis of seminiferous tubules
  - ↓ testosterone →↑LH→↑Estrogen

Turner Syndrome [Female] (45, XO)

- Turner syndrome is a disorder that occurs when there is complete or partial monosomy of the X chromosome.
- Karyotype XO (45, X) is characteristic.
- **Findings:**
  - Manifested by females
  - Female hypogondisam
  - Replacement of the ovaries by fibrous streaks
  - Infantile genitalia and poor breast development
  - Short stature, webbed neck, shield-like chest
  - Ovarian dysgenesis
  - ↓ Estrogen leads to →↑ LH, FSH.
- **Other Findings**
  - Lymphedema of the extremities and neck (result in webbed neck or **Cystic hygroma**)
  - Coarctation of the aorta (femoral < brachial pulse),
  - Turner syndrome is also often associated with autoantibody-mediated hypothyroidism.
  - Horseshoe kidney.
  - Most common cause of 1° amenorrhea.
  - No Barr body.

XYY syndrome or Double Y males (XYY)	• Increased frequency among criminals • Characteristics include tallness, severe acne, and only rarely mild mental retardation

Abnormalities Due to Increased Numbers of Trinucleotide Repeats

- These diseases may show genetic anticipation → that is the repeats often increases from generation to generation and is associated with earlier onset and more severe manifestations in successive generations
- Examples include (mnemonic: **Try** (trinucleotide) **hunting** for **my fragile** cage eggs)
  - **Hunting**ton disease (CAG)
  - **My**otonic dystrophy (CTG)
  - **Fragile** X syndrome (CGG)

Disease Name	Explanation	Mnemonic
HUNTington disease	• Trinucleotide repeat: **CAG** • Chromosomal mapping of affected gene: Chromosome **4** • **C**audate has ↓ **A**Ch and **G**ABA • Clinical features: ◦ Chorea, ◦ Athetosis ◦ Aggression ◦ Depression ◦ Dementia	You **HUNT** animals and put them in the **CAG**e: Huntington Disease CAG Cage has **4** letters.
Myotonic dystrophy	• Trinucleotide repeat: **CTG** • Chromosomal mapping of affected gene: Chromosome **19** • Clinical features: ◦ **C**ataracts ◦ **T**oupee (early balding in men), ◦ **G**onadal atrophy	You **SEE** **T**onic **G**estures dystrophia myotonica has **19** letters
Fragile X syndrome	• Trinucleotide repeat: **CGG** • Chromosomal mapping of affected gene: **X** chromosome (fragile X) • Clinical features and Pathophysiology: (everything is big) • Clinical features: ◦ **C**hin (protruding), ◦ **G**iant Gonads ◦ Ataxic **GAAit** ◦ Thick brain: **Mental retardation (2nd most common genetic cause of mental retardation after Down's syndrome).**	You **SEE** a **G**ross **G**uy: **CGG**

Disorders Associated With Genomic Imprinting

- At some loci, only one allele is active; the other is inactive (imprinted/inactivated by methylation).
- With one allele inactivated, deletion of the active allele → disease.
- Examples include: Prader-Willi and Angelman syndromes

Prader-Willi syndrome	**Angel*M*an syndrome**
• Due to mutation or deletion of genes on chromosome 15.	• Due to mutation or deletion of genes on chromosome 15.
• Maternal imprinting: gene from mom is normally silent and **P**aternal gene is deleted/mutated (two maternally imprinted genes are received; no paternal gene received)	• Paternal imprinting: gene from dad is normally silent and **M**aternal gene is deleted/mutated. (two paternally imprinted genes are received; no maternal gene received)

• Results in • Hyperphagia leading to obesity and diabetes • Intellectual disability • Hypogonadism	• Results in • Inappropriate laughter ("happy puppet"). • Intellectual disability. • Seizures and ataxia

Modes of Inheritance

Autosomal dominant inheritance	Autosomal recessive inheritance	X-linked recessive inheritance
• One heterozygous parent carries a gene (associated with disorder) and the other parent is normal.	• With 2 carrier (heterozygous) parents • Typically, the parents of an affected individual are not affected but are gene carriers.	• Female parent is carrier and male parent is unaffected
• One half of the children are expected to be affected	• On average • ¼ of children will be affected (homozygous). • ½ of children will be carriers • ¼ of children will be neither affected nor carriers.	• One in two children will be affected • Male children who get the affected x chromosome phenotypically manifest the disorder • Female children are carriers.carriers.
• Diseases are most Often due to defects in structural genes.	• Often due to enzyme deficiencies. • These include most inborn errors of metabolism	• Due to Enzyme deficiencies that are exceptions from autosomal recessive pattern

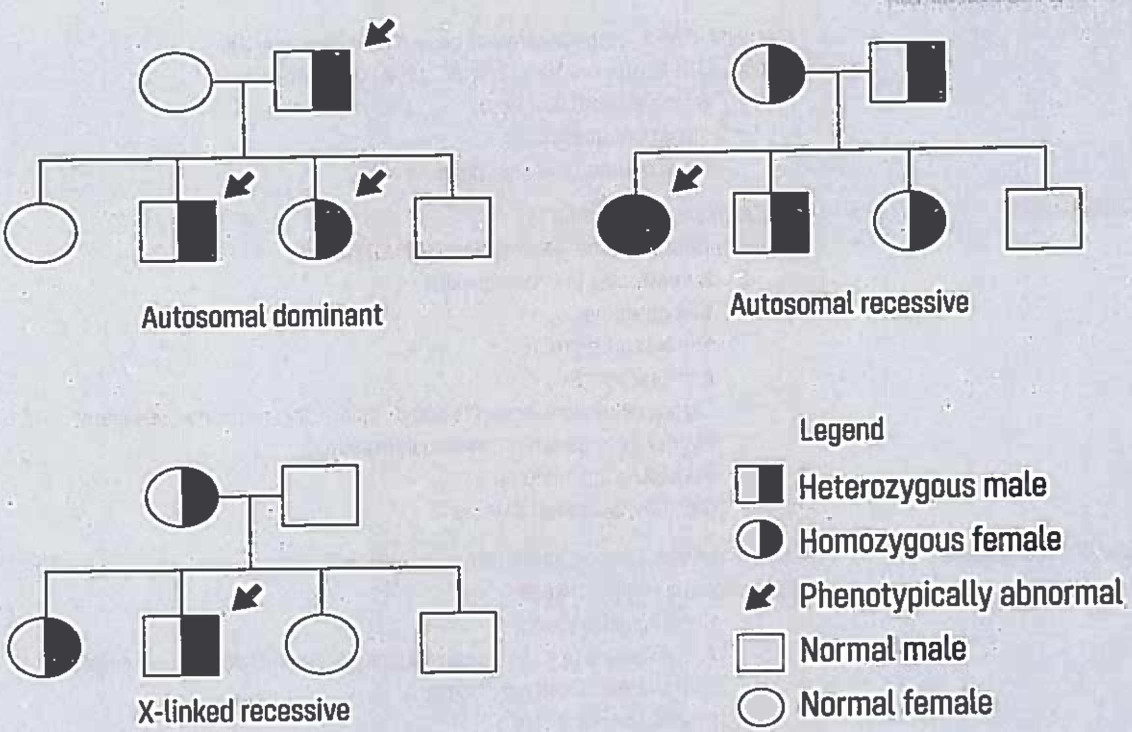


FIGURE 4-1 Modes of inheritance.

Autosomal Dominant Disorders

Mnemonic: Arrogant **Marfan HuNTS Vulnerable Families**

Adult polycystic kidney disease	• Most common hereditary renal disorder. • Characterized by numerous bilateral cysts • Clinically manifest between 20 and 40 years of age even though the genetic defect is present at birth
Marfan syndrome	• Connective tissue disorder due to deficiency of fibrillin. Characteristics include defects in · Skeletal → tall and thin, hyperextensible joints, spider-like fingers (arachnodactyly) · Visual → Dislocation of the ocular lens (ectopia lentis) · Cardiovascular → aortic dissection
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)	• Localized telangiectases of the skin and mucous membranes • Recurrent hemorrhage from these lesions
Hereditary spherocytosis	• Erythrocyte membrane defect → spheroidal erythrocytes that are sequestered and destroyed in the spleen, producing hemolytic anemia
Neurofibromatosis type I (von Recklinghausen disease) 	• Mutation in NF1 tumor suppressor gene on chromosome **17** (**17** letters in "von Recklinghausen") • Findings: · Multiple neurofibromas in skin · Café-au-lait spots (shown in fig) · Optic nerve gliomas · Lisch nodules (pigmented iris hamartomas)
Neurofibromatosis type II	• Mutation in NF**2** tumor suppressor gene on chromosome **22**. • Findings: (NF**2** affects **2** ears, **2** eyes, and **2** parts of the brain) · Bilateral vestibular nerve · Juvenile cataracts · Meningiomas, and ependymomas.
Tuberous **S**clerosis	• Mutation on chromosome 16 • Characteristics include (Mnemonics: **HAMARTOMAS**) · **H**amartomas in CNS and skin · **A**ngiofibromas · **M**itral regurgitation; · **A**sh-leaf spotS · Cardiac **R**habdomyoma; (**T**uberous sclerosis); autosomal d**O**minant; · **M**ental Retardation (intellectual disability); · Renal **A**ngiomyolipoma · **S**eizures, **S**hagreen patches.
Von Hippel-Lindau disease	• Deletion of VHL gene on chromosome 3p (VHL = 3 letters). • Characteristics include: **HARP:** · **H**emangioblastomas; · **A**ngiomatosis (e.g., cavernous hemangiomas in skin, mucosa, organs) · bilateral **R**enal cell carcinomas; · **P**heochromocytomas.
Familial hypercholesterolemia	• Defective low-density lipoprotein (LDL) receptors • As a result, decreased transport of LDL cholesterol into cells, which causes hypercholesterolemia • Manifested by ↑ atherosclerosis, xanthomas

Autosomal Recessive Disorders

Lysosomal Storage Disease

Disorder	Enzyme Deficiency	Accumulation	Characteristics
Tay-Sachs disease	Hexosaminidase A	Gm2 ganglioside (accumulation especially in neurons)	• CNS degeneration • Blindness (amaurosis). • Characteristic cherry-red spot in the macula.

Gaucher disease	Glucocerebrosidase	Glucocerebroside (Disorder of lipid metabolism)	• Gaucher cells (lipid-laden macrophages resembling crumpled tissue paper).
			• Type I, or adult Gaucher disease
			  • Hepatosplenomegaly
			  • Avascular necrosis of femur, normal life span possible
			• Type II, or infantile Gaucher disease
			  • CNS involvement and death before 1 years of age*
			• Type III, or juvenile Gaucher disease
			  • Involves both the brain and the viscera
			  • But is less severe than type II

Niemann-Pick disease	Sphingomyelinase	Sphingomyelin (Defect in a gene involved in cholesterol transport With cholesterol accumulation within phagocytes)	• Progressive neurodegeneration, • Hepatosplenomegaly • Foamy histiocytes," containing sphingomyelin, • lipid-laden macrophages • "Cherry-red" spot on macula like Tay-Sachs disease
Hurler syndrome	α-L-iduronidase	Heparan sulfate, dermatan Sulfate (Accumulations of the mucopolysaccharides heparan sulfate and dermatan Sulfate in the heart, brain, liver, and other organs)	• Hepatosplenomegaly • Dwarfism • Corneal clouding • Progressive mental retardation • The syndrome is clinically similar to, but should not be confused with, Hunter Syndrome, which is an X-linked recessive disorder

Glycogen Storage Diseases

Disorder	Enzyme Deficiency	Accumulation	Characteristics
Von Gierke disease (type I glycogenosis)	Glucose-6-phosphatase	Glycogen	• Accumulation of glycogen in the liver and kidney • characteristics include hepatomegaly and sometimes intractable hypoglycemia
Pompe disease (type II glycogenosis)	α-1,4-glucosidase	Glycogen	• Accumulation of glycogen in the liver, heart, and skeletal muscle. • Characteristics include cardiomegaly, muscle hypotonia, and splenomegaly

Cori disease (type III glycogenosis)	Amylo-1,6-glucosidase	Glycogen	• Accumulation of glycogen in the liver, heart, or skeletal muscle. • Characteristics include stunted growth, hepatomegaly, and hypoglycemia
McArdle syndrome (type V glycogenosis)	Muscle phosphorylase	Glycogen	• Glycogen accumulation in skeletal muscle. • This disease produces painful muscle cramps and muscle weakness following exercise. • Mnemonic= **M**cArdle = **M**uscle

Autosomal Recessive Disorders (continued)

Disorders of Carbohydrate Metabolism

Disorder	Enzyme Deficiency	Accumulation	Characteristics
Galactosemia	Galactose-1-phosphate uridyl transferase	Galactose-1-phosphate (Accumulation in tissues)	• Infantile cataract • Mental retardation • Progressive hepatic failure leading to cirrhosis and death.

Disorders of Amino Acid Metabolism

Disorder	Enzyme Deficiency	Accumulation	Characteristics

Phenylketonuria	Phenylalanine hydroxylase	Phenylalanine and its degradation products	• Phenylalanine hydroxylase deficiency results in failure of conversion of phenylalanine to tyrosine in the liver
			• Characteristics
			  • Progressive mental deterioration
			  • Seizures, hyperactivity, and other neurologic abnormalities
			  • Decreased pigmentation of hair, eyes, and skin (children are characteristically blond and blue-eyed)
			  • Mousy or musty body odor from phenylacetic acid in urine and sweat.
			• Screening tests for serum phenylalanine or urinary catabolites are usually performed on the third or fourth day of life.
			• Earlier screening may result in false-negative results.

Alkaptonuria	Homogentisic oxidase	Homogentisic acid	• The cause is incomplete metabolism of phenylalanine and tyrosine due to deficiency of homogentisic oxidase, leading to accumulation and urinary excretion of homogentisic acid.
			• Characteristics include
			  • urine that turns dark and finally black on standing;
			  • **Ochronosis**, dark pigmentation of fibrous tissues and cartilage

Cystic Fibrosis

CauseCause	• Mutation in the CFTR (cystic fibrosis transmembrane conductance regulator) gene on chromosome 7
Pathophysiology	• This gene codes for a membrane protein that facilitates the movement of chloride and other ions across membranes
Characteristics	• Malfunction of exocrine glands, resulting in increased viscosity of mucus and increased chloride concentration in sweat and tears.
Complications	• Recurrent pulmonary infections (e.g., S aureus [early infancy], P aeruginosa [adolescence]), chronic bronchitis and bronchiectasis • Pancreatic insufficiency, malabsorption with steatorrhea, fat-soluble vitamin deficiencies (A, D, E, K), biliary cirrhosis, liver disease. • Meconium ileus in newborns. • Infertility in men (absence of vas deferens, spermatogenesis may be unaffected) and subfertility in women (amenorrhea, abnormally thick cervical mucus).
Diagnosis	• Sweat chloride test ↑Cl− concentration (> 60 mEq/L) in sweat is diagnostic (Secretion by sweat glands of chloride and sodium is normal, but their reabsorption by sweat ducts is impaired) • Newborn Screening → Immunoreactive Trypsinogen (IRT) assay

X-linked recessive disorders

Mnemonic: **HUNTER F**emale **L**iving **D**owntown **G**ot **H**emophilia

Disorder	Enzyme Deficiency	Accumulation	Characteristics

Hunter syndrome	I-Iduronosulfate sulfatase	Heparan sulfate, dermatan sulfate	• Lysosomal storage disease, a form of mucopolysaccharidosis clinically similar to, but less severe than, Hurler syndrome.
			• Characteristics
			  • Hepatosplenomegaly
			  • Retinal degeneration,
			  • Joint stiffness
			  • Mild mental retardation

Fabry disease	α-Galactosidase A	Ceramide trihexoside	• lysosomal storage disease
			• Characteristics
			  • Skin lesions (angiokeratomas) over the lower trunk
			  • Febrile episodes
			  • Severe burning pain in the extremities

Lesch-Nyhan syndrome	HGPRT (hypoxanthine-guanine phosphoribosyltransferase)	Uric acid	• Characteristics (Mnemonic- HGPRT)
			  • **H**yperuricemia
			  • **G**out
			  • **P**issed off (aggression, self-mutilation)
			  • **R**etardation (intellectual disability)
			  • Dys**T**onia

Duchenne muscular dystrophy	Dystrophin		
G6PD deficiency	G6PD		
Classic Hemophilia (hemophilia A)	Factor VIII		• Hemorrhage from minor wounds and trauma, bleeding from oral mucosa, hematuria, and hemarthroses.

Disorders of Sexual Differentiation

True hermaphrodite	This rare condition is characterized by both ovarian and testicular tissue, with ambiguous external genitalia and both X and Y chromosomes
Pseudohermaphrodite	This organism has gonads of only one sex, but the appearance of the external genitalia does not correspond to the gonads present.

Male Pseudohermaphrodite

- Genotype: 46XY
- The gonads are testes, but the external genitalia are not clearly male.
- Causes:
  - Tissue resistance to androgens (testicular feminization) is the most common cause
  - Defects in testosterone synthesis
  - Hormones administered to the mother during

Female Pseudohermaphrodite

- Genotype: 46XX
- The gonads are ovaries, but the external genitalia are not clearly female.
- Causes:
  - The condition is most often caused by increased androgenic hormones from congenital adrenal hyperplasia
  - An androgen-secreting adrenal or ovarian tumor in the mother
  - Hormones administered to the mother during pregnancypregnancy

Genetic Disorders by Chromosome

Chromosome	Examples
3	• von Hippel-Lindau disease, renal cell carcinoma
4	• ADPKD, Achondroplasia, Huntington disease
5	• Cri-du-chat syndrome, familial adenomatous polyposis
6	• Hemochromatosis
7	• Williams syndrome, cystic fibrosis
9	• Friedreich ataxia
11	• Wilms tumor, β-globin gene defects (e.g., sickle cell disease, β-thalassemia)
13	• Patau syndrome, Wilson disease, retinoblastoma (RB1)
15	• Prader-Willi syndrome, Angelman syndrome, Marfan syndrome
16	• α-globin gene defects (e.g., α-thalassemia)
17	• Neurofibromatosis type 1
18	• Edwards syndrome
21	• Down syndrome
21	• Neurofibromatosis type 2, DiGeorge syndrome (22q11)
X	• Fragile X syndrome, X-linked agammaglobulinemia, Klinefelter syndrome (XXY)

Chapter 5: Immunology

Immune System Organs

Primary Organs	• Bone marrow—immune cell production, B cell maturation • Thymus—T cell maturation
Secondary Organs	• Spleen, lymph nodes, tonsils, Peyer patches • Allow immune cells to interact with antigen

Cells of the Immune System

Lymphocytes

- These include B cells, T cells, and natural killer (NK) cells
- Natural Killer Cells:
  - Approximately 15% of circulating peripheral blood lymphocytes

B- cells	T-cells
• Originate from stem cells in the bone marrow	• Originate from stem cells in the bone marrow
• Differentiate in the bone marrow and peripherally (**B** cells= **B**one marrow)	• Differentiate in the thymus (**T**-cells= **T**hymus)
• They populate the germinal centers of • Lymph node	• They populate the paracortical and deep medullary areas of lymph nodes
• The presence of surface immunoglobulin is characteristic	• No surface immunoglobins
• Approximately 15% of circulating peripheral blood lymphocytes	• Approximately 70% of circulating peripheral blood lymphocytes
• Humoral immunity	• Cell mediated immunity

Further subdivided into

- **CD4+ T cells**
  - About 60%
  - Associated with MHC-II
  - Help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes.
- **CD8+ T cells**
  - About 30%
  - Directly kill virus-infected cells.
  - Associated with MHC-I

Rule of 8: MHC **II** × CD**4** = **8**; MHC **I** × CD**8** = **8**.

Macrophages	• Macrophages secrete a variety of cytokines, including interleukin-1 (IL-1), as well as other products, such as acid hydrolases, neutral proteases, and prostaglandins. • In addition, they process and present antigen (along with MHC-II) to CD4+ T cells. • Macrophages also participate in delayed hypersensitivity reactions.
Dendritic cells	• Characterized by dendritic cytoplasmic processes • Dendritic cells express large quantities of cell surface MHC-II
Langerhans cells of the skin	• Ultrastructural characteristics include the presence of Birbeck granules, tennis racket shaped cytoplasmic structures. • Langerhans cells of skin express MHC-II antigens & are antigen-presenting cells.

Important Cytokines

- Mnemonic "**Hot T-Bone stEAk**"
  - IL-1: fever (hot)
  - IL-2: stimulates T cells
  - IL-3: stimulates Bone marrow
  - IL-4: stimulates IgE
  - IL-5: stimulates IgA
  - IL-6: stimulates aKute-phase protein production

IL-1, IL-6, and TNF-α can mediate sepsis

Secreted by Macrophages

Interleukin-1	• MCauses fever, acute inflammation
Interleukin-6	• Causes fever and stimulates production of acute phase proteins.
Interleukin-8	• Major chemotactic factor for neutrophils
Interleukin-12	• Induces differentiation of T cells into Th1 cells.
Tumor necrosis factor-α	• Causes cachexia in malignancy. • Maintains granulomas in TB.

Secreted by All T-Cells

Interleukin-2	• Stimulates proliferation of T cells, B cells, and NK cells
Interleukin-3	• Supports growth and differentiation of bone marrow stem cells. • Functions like GM-CSF.

From Th1 Cells

Interferon-γ	• Secreted by NK cells and T cells in response to antigen or IL-12 from macrophages • Stimulates macrophages to kill phagocytosed pathogens. • Inhibits differentiation of Th2 cells.

From Th2 Cells

Interleukin-4	• Induces differentiation of T cells into Th2 cells. • Promotes growth of B cells. • Enhances class switching to IgE and IgG.
Interleukin-5	• Promotes growth and differentiation of B cells. • Enhances class switching to IgA. • Stimulates growth and differentiation of eosinophils
Interleukin-10	• Attenuates inflammatory response. • Decreases expression of MHC class II and Th1 cytokines. • Inhibits activated macrophages and dendritic cells. • Also secreted by regulatory T cells

Innate Versus Acquired Immunity

Innate Immunity	Acquired Immunity
• Mediated by Neutrophils, macrophages, monocytes, natural killer (NK) cells	• Mediated by B and T lymphocytes
• Occurs rapidly (minutes to hours)	• These are not immediate and take time for optimal reactivity
• Secretes Lysozyme, complement, C-reactive protein(CRP), Defensins	• Secretes Immunoglobulins
• Associated with Toll-like receptors • No memory response	• Memory cells → stronger, quicker immune response

Human Leukocyte Antigen System

- The HLA system consists of a group of related proteins referred to as HLA antigens.
- The genes that code for HLA antigens are called histocompatibility genes and are localized to a region on the short arm of chromosome 6, known as the Major Histocompatibility Complex (MHC).
- The HLA system is important in organ transplantation, where HLA typing and matching of donor and recipient are now widely used to predict tissue compatibility
- Divided into two major classes

Class I antigens	Class II antigens
Mnemonic: class I has 1 letter and associated with MHC I	Mnemonic: class II has 2 letter and associated with MHC II
• Include the HLA-**A**, HLA-**B**, and HLA-**C** antigens, which are found on almost all human cells.	• The HLA-**DP**, HLA-**DQ**, and HLA-**DR** are chiefly found on immunocompetent cells, including macrophages.
• Class I antigens are the principal antigens involved in tissue graft rejection	

HLA Subtypes Associated With Diseases

B27 (**PAIR**)	Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis	**PAIR**. Also known as seronegative arthropathies
DQ2/DQ8	Celiac disease (**gluten** sensitive enteropathy)	I ate (**8**) too (**2**) much **gluten** at **D**airy **Q**ueen
Dr2	**Multiple** sclerosis, **hay** fever, SLE, Good**pasture** syndrome	**Multiple hay pastures** have **d**i**r**t.
Dr**3**	Diabetes mellitus type 1, **SLE**, Graves' disease, Hashimoto thyroiditis, Addison disease	**2-3, S-L-E**
Dr**4**	**Rheumatoid arthritis**, diabetes mellitus type 1, Addison disease	There are **4** walls in a "**rheum**" (room).
Dr5	Pernicious anemia vitamin B12 deficiency Hashimoto thyroiditis	

Immunoglobins

IgA	IgG	IgM	IgE	IgD
• Released into secretions (tears, saliva, mucus) and breast milk.	• Smallest	• Largest • (Macro= IgM)	• Binds mast cells and basophils	• Unclear function.

• Most produced antibody overall, but has lower serum concentrations	• highest serum concentration (maGor=IgG)	•	• Lowest serum concentration	• Found on surface of many B cells and in serum.
• Produced in GI tract (e.g., by Peyer patches) and protects against gut infections (e.g.Giardia)	• Warm antibody	• Cold antibody		
	• Crosses placenta (**Gestation=IgG**)	• Early or primary immune response (i**MM**ediate=Ig**M**)		

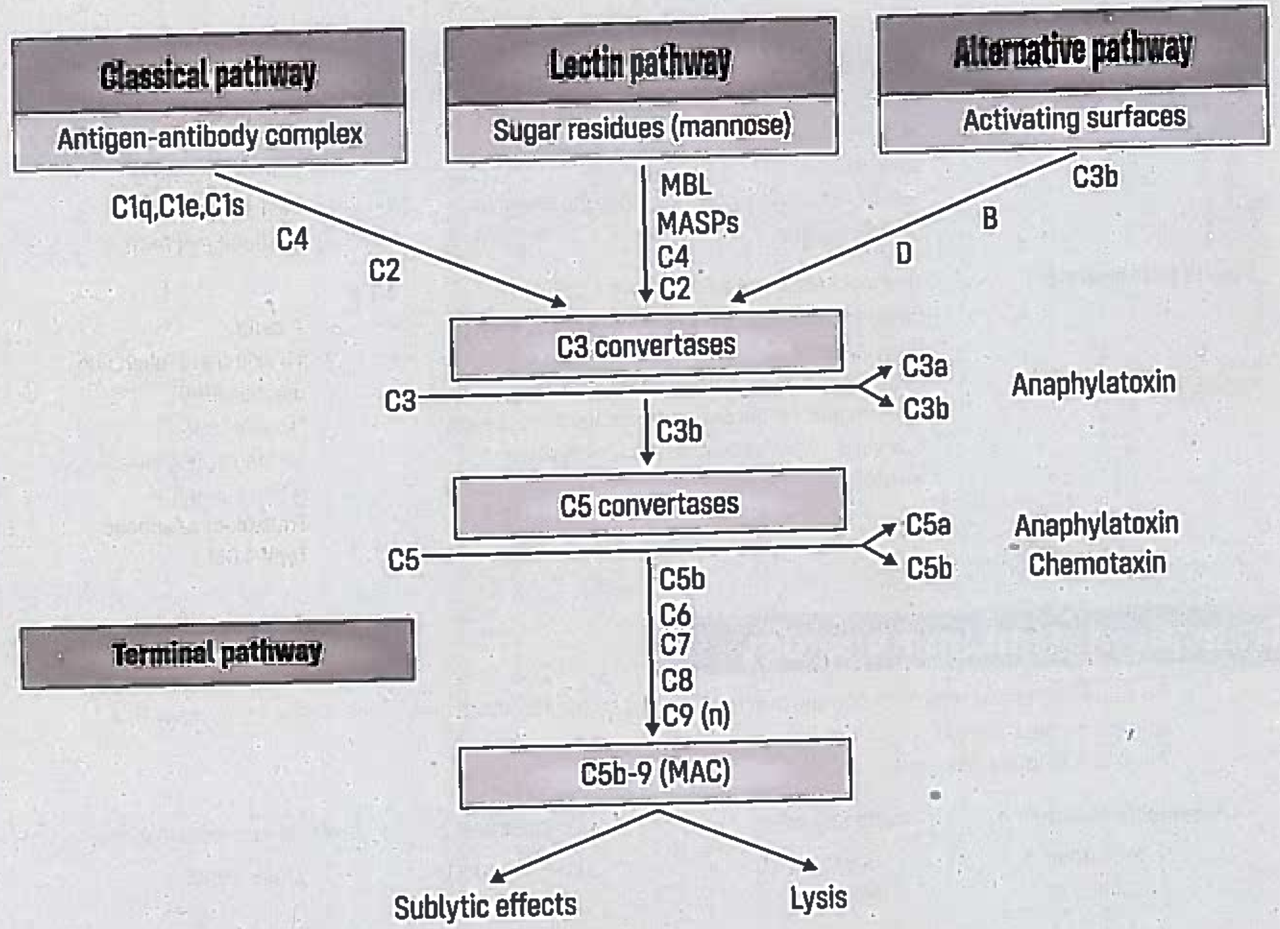
Complement System

- This system consists of about 20 plasma proteins and their products, which can be activated by way of the classic or alternate pathway to form a final product
- Both classic pathway and alternate pathway, form a final product—the membrane attack complex that lyses targeted cells.

Classic Pathway	**Alternate Pathway**
• Initiated by reaction with antigen-antibody complexes • IgG or IgM mediated (**GM** makes **classic** cars)	• Initiated directly by nonimmunologic stimuli, such as invading microorganisms
	• It bypasses the initial stages of the classic pathway

Functions

- Fab portion is for antigen binding fragment
- Fc portion is for complement binding
- **C3b** and IgG—Opsonization. (**C3b binds bacteria**)
- C3a, C4a, C5a—anaphylaxis.
- C5a—neutrophil chemotaxis.
- C5b-9—cytolysis by Membrane attack complex



Mechanisms of Immune Injury

- Four types ------(ACID)
  - Anaphylactic and Atopic (type I),
  - Cytotoxic (antibody mediated, type II),
  - Immune complex (type III),
  - Delayed (cell mediated, type IV) (ACID).
- Types I, II, and III require the active production of antibody by plasma cells (terminally differentiated B cells).
- Type IV is mediated by the interaction of T cells and macrophages

Hypersensitivity Type	Mechanism	Examples
Type I (immediate or anaphylactic) First (type) and Fast (anaphylaxis)	Antigen reacts with IgE bound to surface of basophils or tissue mast cells, causing degranulation with release of histamine and other substances, many of which are vasoactive, smooth muscle spasm-inducing, or chemotactic	• Hay fever • Allergic asthma • Hives • Anaphylactic shock
Type II (antibody-mediated or cytotoxic)	Antibodies react with antigens that are intrinsic components of cell membrane or other structures, such as basement membranes, resulting in direct damage. complement mediated increased susceptibility to phagocytosis, or antibody dependent cell-mediated cytotoxicity; also may be caused by inactivation of cell-surface receptors by anti-receptor antibodies	• Autoimmune-hemolytic anemia • Immune thrombocytopenic purpura • Transfusion reactions • Hemolytic disease of the newborn • Goodpasture syndrome • Rheumatic fever • Hyperacute transplant rejection • Myasthenia gravis • Graves' disease

Type III (immune complex)	Immune complex—antigen-antibody (IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes. Can be associated with vasculitis and systemic manifestations.	• Serum sickness • Arthus reaction • SLE • Polyarteritis nodosa • Post streptococcal glomerulonephritis
Type IV (cell-mediated)	Two mechanisms, each involving T cells: Direct cell cytotoxicity: CD8+ cytotoxic T-cells kill targeted cells. Delayed-type hypersensitivity: sensitized Cd4+ helper T cells encounter antigen and release cytokines → inflammation and macrophage activation.	**6 T'S** • T-cells • TB skin test (Tuberculin reaction/PPD) • (Touch) contact dermatitis (e.g. poison ivy, nickel allergy) • Transplant rejections • Type-1 DM

Transplantation Immunology

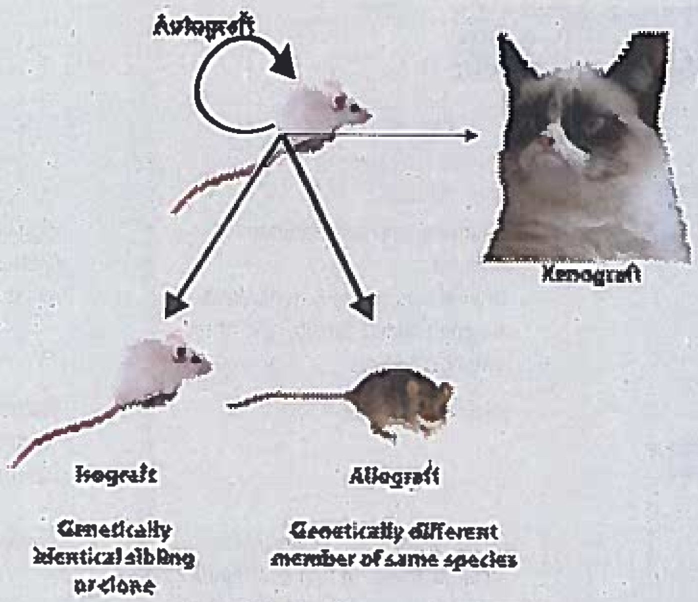
- For a successful graft, donor and recipient must be matched for ABO blood groups and ideally, for as many HLA antigens as possible.
- Types of transplant rejection.

Hyperacute Rejection	Acute Rejection	Chronic Rejection	Graft-Versus-Host Disease.
• Onset within minutes	• Onset days to weeks	• Onset months to years	• Onset varies
• Antibody-mediated • Occurs in the presence of preexisting antibody to donor antigens.	• T cell-mediated. • Rejection generally occurs after transplantation	• Antibody-mediated vascular damage. • Rejection after an otherwise successful transplantation	• This is a significant problem in bone marrow transplantation because immunocompetent cells are transplanted in this procedure. • It can also be caused by whole blood transfusion in patients with severe combined immunodeficiency (SCID).

• Localized Arthus reaction characterized by acute inflammation, fibrinoid necrosis of small vessels, and extensive thrombosis.	• Characterized by infiltration of lymphocytes and macrophages.	• Characterized histologically by marked vascular fibrointimal proliferation.	• The rejection of "foreign" host cells by engrafted T and B cells is characteristic.
			  • CD8+ T cells from graft directly damage host cells.
			  • Cytokines from graft CD4+ T cells recruit macrophages, which damage host cells.

Grafts

- Autograft → From self.
- Isograft (Syngeneic graft) → from identical twin or clone.
- Allograft → From nonidentical individual of same species.
- Xenograft → From different species.



Immunodeficiency Diseases

B- Cell Disorders

Disease	Explanation	Findings
X-linked (Bruton) agammaglobulinemia	• Occurs in male • Manifest clinically after 6 months of age because of the persistence of maternal antibodies • Defect in B-cell tyrosine kinase (BTK) gene → leading to failure of maturation of pre B-cells to B-cells	• Absent B cells in peripheral blood • ↓ immunoglobins of all classes • Recurrent bacterial infections • Resistance to viral and fungal infections is not affected with exception of enteroviruses such as coxsackie and ECHO virus
Isolated IgA deficiency	• Most common inherited B-cell defect • Most often Asymptomatic, • But it may be characterized by occasional Anaphylactic reactions to transfused blood products; this can be prevented by "washing" of the products to remove immunoglobulins prior to transfusion.	• ↓IgA with normal IgG, IgM levels.
Common variable immunodeficiency.	• Failure of terminal B-cell maturation	• ↓ Plasma cells, • ↓ Immunoglobulins. • Recurrent bacterial infections

T- Cell Disorders

Disease	Explanation	Findings
DiGeorge syndrome (Thymic hypoplasia)	• Deletion of 22q11 • Failure to develop 3rd and 4th pharyngeal pouches → absent thymus and parathyroids.	• Tetany • Recurrent viral and fungal infections Hypoparathyroidism with hypocalcemia. • CATCH 22 → Cardiac defects, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia, and microdeletion of chromosome 22.

B- and T-cell Disorders

Disease	Explanation	Findings
Severe combined immunodeficiency disease (SCID).	• Marked deficiency of both B and T cells manifests • ↓humoral and cell-mediated immunity. • Thymic hypoplasia & Hypoplasia of lymph nodes, tonsils, and other lymphoid tissues	• Severe infections (bacterial, viral, and fungal) • High incidence of malignancy • Graft-versus-host disease as a result of blood transfusions
Wiskott-Aldrich syndrome (Immunodeficiency with thrombocytopenia and eczema)	• X -linked disorder	• WATER → Wiskott-Aldrich, Thrombocytopenia, Eczema, Recurrent infections
Hyper-IgM syndrome	• It is characterized by normal or elevated levels of IgM, but failure of isotype switching to IgG, IgA, or IgE.	• ↑ pyogenic infections

Amyloidosis

- Amyloidosis refers to accumulation of insoluble fibrillar proteins that form β-pleated sheaths, two types
- Light Microscopy—Congo red stain shows apple-green birefringence

Primary (AL) amyloidosis	Secondary (AA) amyloidosis
Most common → in developed world.	Less common in developed countries
Due to deposition of proteins from Ig Light chains	Occurs in patients with long-standing neoplasia or inflammation and is associated with serum amyloid protein called AA protein
Can occur as a plasma cell disorder or associated with multiple myeloma and Waldenström macroglobulinemia,	it is often seen in concert with tuberculosis, leprosy, RA

Other Forms of Amyloidosis

- Alzheimer disease
  - Characterized by deposits of an amyloid protein referred to as A4 amyloid, or amyloid b-protein, which differs from AL, AA, and transthyretin-derived amyloid.
  - The gene that codes for the protein precursors of A4 amyloid has been localized to chromosome 21
- Dialysis-associated amyloidosis
  - Is characterized by amyloid deposits in the joints of patients who have undergone hemodialysis for several years.
  - The amyloid is derived from β-microglobulin, a protein not readily filtered by the dialysis membrane

Chapter 6: Neoplasia

Neoplastic Progression.

Dysplasia

- Pleomorphism → Abnormal proliferation of cells with loss of size, shape, and orientation

Carcinoma in situ/ preinvasive

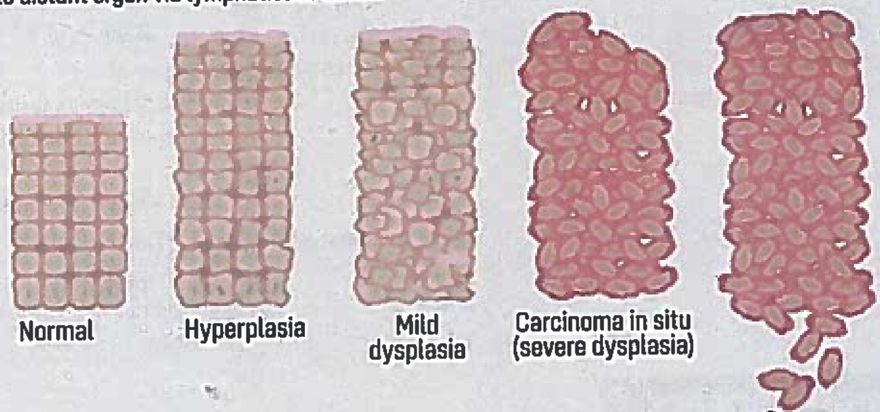
- Neoplastic cells have not invaded the intact basement membrane.
- ↑ Nuclear: cytoplasmic ratio and clumped chromatin.

Invasive carcinoma

- Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases).
- Cell-cell contacts lost by inactivation of E-cadherin.

Metastasis

- Spread to distant organ via lymphatics or blood.



Carcinoma Vs. Sarcoma

Type	Carcinoma	Sarcoma
Origin	• Malignant tumor of epithelial origin	• Malignant tumor of mesenchymal origin
Frequency	• More common	• Less common
Examples	• Squamous cell carcinoma • Transitional cell carcinoma • Adenocarcinoma	• It is often used with a prefix that denotes the tissue of origin of the tumor e.g. • Osteosarcoma (bone) • Rhabdomyosarcoma (skeletal muscle) • Leiomyosarcoma (smooth muscle) • Liposarcoma (fatty tissue).

Benign Vs. Malignant Tumor

- Benign tumors are well differentiated while malignant ranges from well-diferentiated to undifferentiated
- Benign tumors remain localized while malignant tumors invades (characteristic feature of malignant tumors is invasion)
- Examples

Cell Type	Benign	Malignant
Epithelium	Adenoma, papilloma	Adenocarcinoma, papillary carcinoma
Mesenchyme		
Blood cells		Leukemia, lymphoma
Blood vessels	Hemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Connective tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
Melanocyte	Nevus/mole	Melanoma

Tumor Grade Vs. Stage

Grade	Stage
• it establishes on degree of cellular differentiation and mitotic activity on histology	• it establishes on degree of ◦ Site and size of primary lesion ◦ Extent of spread of primary lesion to regional lymph nodes ◦ Presence or absence of metastasis
	• Methods of staging (TNM system) ◦ T= size of primary tumor ◦ N=regional lymph node involvement ◦ M=metastasis

Most Common Cancers

- Skin cancer is the most common cancer overall (basal > squamous > melanoma)

Men	Women	Children
1. Prostate	1. Breast	1. Leukemia
2. Lung	2. Lung	2. Brain and CNS
3. Colon/rectum	3. Colon/rectum	3. Neuroblastoma

Paraneoplastic Syndromes

- Caused by ectopic production of hormones or chemical substances inducing effects similar to those of a given hormone

Manifestation	Description/Mechanism	Most Commonly Associated Cancer(S)
Cushing syndrome	↑ ACTH	• Small Cell Carcinoma of The Lung.
SIADH	↑ ADH	• Small Cell Carcinoma of The Lung.
Hypercalcemia	↑ PTHrP (parathyroid hormone related protein)	• Squamous Cell Carcinomas of Lung • Head, And Neck; Renal, Bladder, Breast, And Ovarian Carcinomas
Hypoglycemia	↑ insulin-like substances	• Hepatocellular Carcinomas
Hyperthyroidism	↑ TSH	• Hydatidiform Moles • Choriocarcinomas
Polycythemia	↑ Erythropoietin	• Renal Cell Carcinoma • Pheochromocytoma

Carcinogens

Carcinogen	OrganExample
Aromatic amines (e.g., benzidine, 2-naphthylamine)	• Bladder → Transitional cell carcinoma
Arsenic	• Liver → Angiosarcoma • Lung → Lung cancer • Skin → Squamous cell carcinoma
Asbestos	• Lung → Bronchogenic carcinoma > mesothelioma
Cigarette smoke	• Bladder → Transitional cell carcinoma • Esophagus → Squamous cell carcinoma/adenocarcinoma • Larynx → Squamous cell carcinoma • Lung → Squamous cell and small cell carcinoma
Aflatoxins (Aspergillus)	• Liver → Hepatocellular carcinoma
Vinyl chloride	• Liver Angiosarcoma

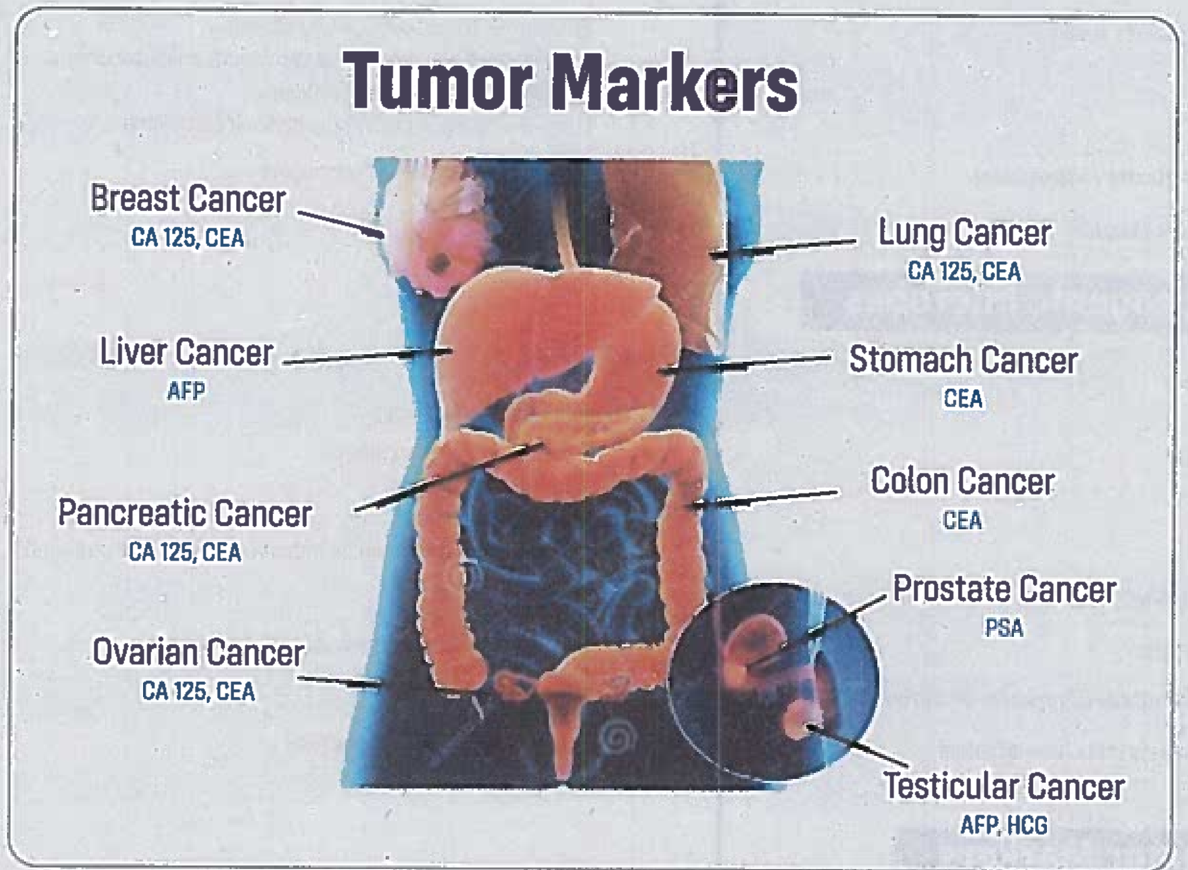
Oncogenic Microbes

HPV	• Cervical carcinoma • Penile/anal carcinoma
EBV	• Nasopharyngeal carcinoma • Burkitt lymphoma • Hodgkin lymphoma • Primary CNS lymphoma (in immunocompromised patients)
HHV-8	• Kaposi sarcoma
H pylori	• Gastric adenocarcinoma and MALT lymphoma
Liver fluke (Clonorchis Sinensis)	• Cholangiocarcinoma
Schistosoma haematobium	• Bladder cancer (squamous cell)

Tumor Markers

- Tumor markers are used to detect recurrence and response to therapy
- For tumor diagnosis use → biopsy

Marker	Associated Cancer	Notes
Alkaline phosphatase	• Bony or liver metastasis • Paget disease of bone	
α-fetoprotein	• Hepatocellular carcinoma. • Yolk sac (endodermal sinus) tumor • Mixed germ cell tumor.	• Normally made by fetus. • Transiently elevated in pregnancy. • High levels→ neural tube defects • Low levels→ Down syndrome.
β-hCG	• Hydatidiform moles • Choriocarcinomas (Gestational trophoblastic disease) • Testicular cancer	• β- hCG is produced by syncytiotrophoblasts of the placenta.
CA 15-3	• Breast cancer	
CA 19-9	• Pancreatic adenocarcinoma	
CA 125	• Ovarian cancer	
CEA	• Colorectal cancer • Pancreatic cancer. • Minor association with breast cancer	
PSA	• Prostate cancer	



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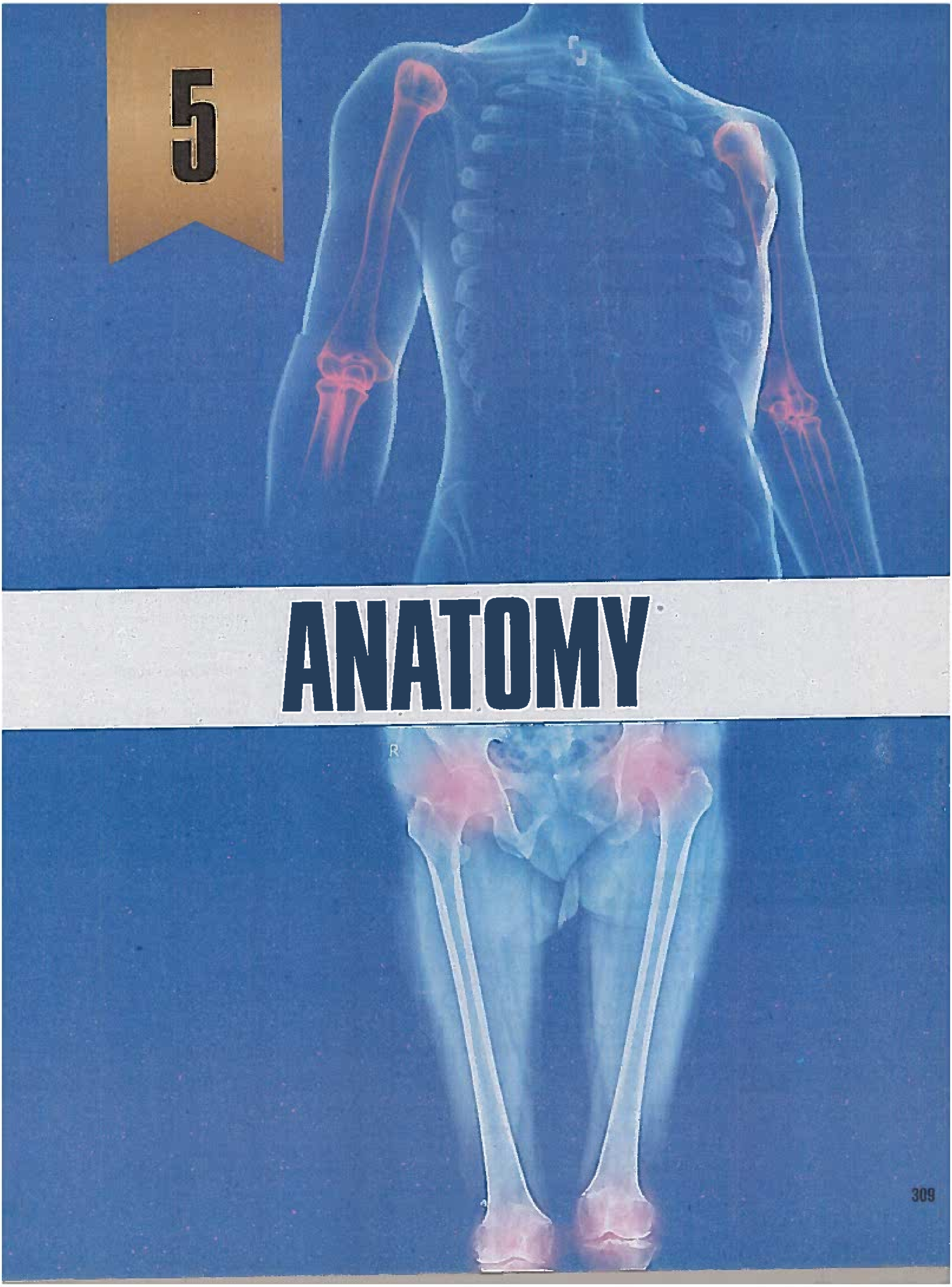
ANATOMY



Chapter 1: Upper Limb

Parts of the Upper Limb

Parts	Subdivision	Bones	Joints
Shoulder region	• Pectoral region on front of chest • Axilla or armpit • Scapular region on back	• Clavicle • Scapula	• Sternoclavicular joint • Acromioclavicular joint
Upper arm		• Humerus	• Shoulder joint
Forearm		• Radius • Ulna	• Elbow joint • Radioulnar joint
Hand	• Wrist	• Carpus, made of 8 carpal bones	• Wrist joint • Intercarpal joints
	• Hand proper	• Metacarpus made of 5 metacarpal bones	• Carpometacarpal joints • Intermetacarpal joints
	• Five digits • First=Thumb Or Pollex • Second= Index Or Forefinger • Third= Middle Finger • Fourth=Ring Finger • Fifth= Little Finger	• 14 phalanges = 2 for thumb and 3 for each finger	• Metacarpophalangeal joints • Proximal and distal interphalangeal joints

BONES OF UPPER LIMB

1. **Clavicle:**
   - Clavicle and scapula forms the shoulder girdle
   - Articulates medially with the sternum and first costal cartilage and laterally with scapula.
   - Medial 2/3→convex forward.
   - Lateral 1/3 → concave forward.
   - It is the only long bone that lies horizontally.
   - It is the first bone to start ossifying and only long bone which ossifies in membrane and has two primary centres of ossification.
2. **Scapula:**
   - Flat triangular bone. On its posterior surface spine of scapula project backwards.
   - Lateral end of spine forms acromion which articulates with clavicle.
   - Supero-lateral angle of scapula forms the glenoid cavity which articulates with the humerus.
   - The coracoid process projects upwards and forward and it provides attachments for muscle and ligaments.
   - Medial to the base of coracoid process is suprascapular notch.
   - The subscapular fossa is the concave anterior surface of the scapula.

- The supraspinous fossa lies above the spine and infraspinous fossa lies below spine on posterior surface of scapula.

3. **Humerus:**
   - The head of the humerus lies at upper end and forms approximately a third of sphere, which articulates with the glenoid cavity of scapula.
   - Immediately below head is the anatomical neck.
   - Below anatomical neck are the greater and lesser tuberosities.
   - Distal to the tuberosities is the surgical neck which is frequently fractured.
   - The deltoid tuberosity is a roughned area approximately halfway down the lateral aspect of the shaft and is for insertion of deltoid muscle.
   - Behind and below the deltoid tuberosity is a spiral groove in which radial nerve lies.
   - The medial and lateral epicondyles lies at the end of humerus.
   - The rounded capitulum articulates with the head of radius and pulley shaped trochlea articulates with trochlear notch of the ulna.
   - Above the trochlea posteriorly is olecranon fossa which receives olecranon process of ulna when elbow joint is extended.

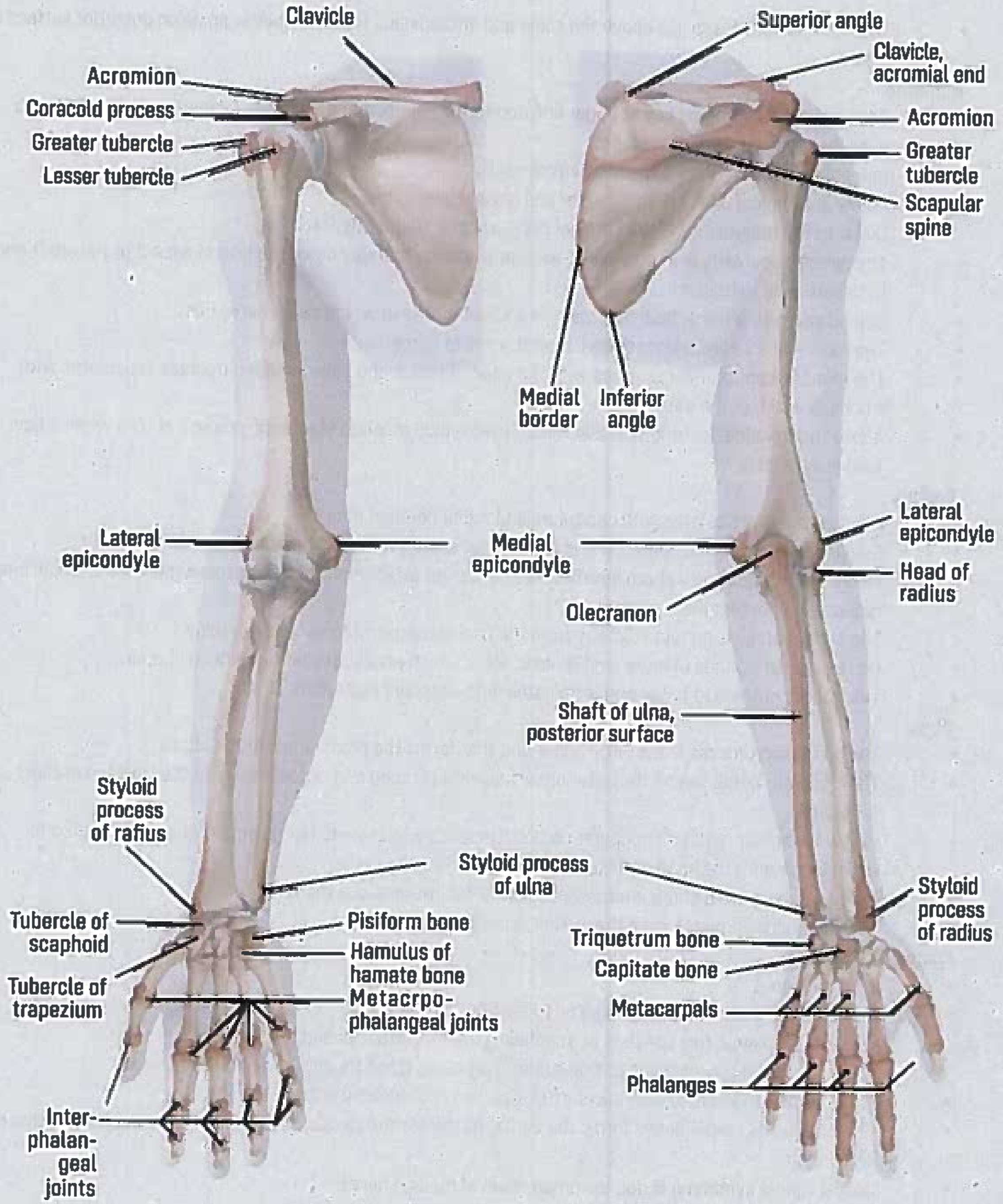
4. **Radius:**
   - Head of radius articulates with capitulum and radial notch of ulna.
   - Below head is neck and below neck is bicipital tuberosity for insertion of biceps brachii muscle.
   - Medially the shaft has a sharp interosseous border for attachment of interosseous membrane which binds radius and ulna together.
   - The styloid process projects distally from the lateral margin of lower end of radius.
   - On the medial surface of lower end is ulnar notch which articulates with the head of ulna.
   - The inferior surface of lower end articulates with scaphoid and lunate bone.

5. **Ulna:**
   - The olecranon process is the large upper end that forms the prominence of the elbow
   - The trochlear notch lies on the anterior surface of olecranon and articulates with the trochlea of the humerus.
   - Below triangular notch is triangular coronoid process which on its lateral surface has radial notch for articulation with the head of radius.
   - Laterally shaft has a sharp interosseous border for interosseous membrane.
   - Styloid process projects from the medial aspect of the head.

6. **Carpal bones:**
   - 8 carpal bones.
   - From lateral to medial (She Looks Too Pretty, Try To Catch Her)
     - Proximal row consists of Scaphoid, Lunate, Triquetral and the Pisiform.
     - Distal row consists of Trapezium, Trapezoid, Capitate and the Hamate.
   - On anterior surface flexor retinaculum is attached that forms a bridge.
   - The bridge and carpal bones forms the carpal tunnel for the passage of median nerve and long flexors of the fingers
   - Carpal tunnel syndrome is due to compression of median nerve.

7. **Metacarpal bones:**
   - 5 metacarpal bones.
   - Bases articulates with carpal bones.
   - Head which form the knuckles articulates with proximal phalanges.

7. **Phalanges:**
   - Total 14, 3 phalanges for each finger but 2 for thumb.



Anterior view.

B Posterior view.

JOINTS OF UPPER LIMB

Shoulder Joint

Articulation	• Head of humerus + glenoid cavity of scapula (Glenohumeral articulation).
Capsule	• Around glenoid labrum and anatomic neck of humerus. • Strengthened by subscapularis muscle anteriorly, supraspinatus muscle superiorly, and infraspinatous muscle and teres minor muscles posteriorly. • Collectively these muscle tendons are called the rotator cuff.

Ligaments:	•	Glenohumeral, transverse humeral, coracohumeral and accessory ligament
Arterial supply:	•	Anterior and posterior circumflex humeral artery. • Suprascapular artery. • Subscapular artery
Nerve supply:	•	Axillary and suprascapular nerves
Important relations	•	Weakest part of joint lies inferiorly because there is little support there and capsule is weakest in that area. • Anteriorly: brachial plexus and axillary vessels. • Inferiorly: axillary nerve and posterior circumflex humeral vessels • Dislocation of joint: subglenoid displacement of head of humerus into quadrangular space can cause damage to axillary nerve indicated by paralysis of deltoid muscle and loss of skin sensation over lower half of deltoid.

Elbow Joint

Articulation	• Trochlea of humerus with trochlear notch of ulna • Capitulum of humerus, with head of radius.
Type	• Synovial hinge joint.
Ligaments	• Lateral collateral ligament: lateral epicondyle of humerus and ulna. • Medial collateral ligament: medial epicondyle of humerus and coronoid process and olecranon process of ulna, it is closely related to ulnar nerve
Arterial supply	• From anastomosis around elbow joint.
Nerve supply	• Median, ulnar and radial nerve
Important relations	• Anteriorly: median nerve and brachial artery. • Medially: ulnar nerve, as it passes behind the medial epicondyle of humerus

Wrist Joint (Radio-Carpal Joint)

Articulation	• Radius + scaphoid, lunate and triquetral bones
Type	• Synovial condyloid joint
Important relations	• Anteriorly: median and ulnar nerve • Laterally: radial artery

Extra:

- Carpometacarpal joint → Synovial saddle joint.
- Metacarpophalangeal joint → Synovial condyloid joint.
- Interphalangeal joint → Synovial hinge joint.

MUSCLES OF UPPER LIMB

Muscles of Pectoral Region

Muscle	Origin	Insertion	Nerve Supply
Pectoralis major	Clavicle, sternum, and upper six costal cartilages	Lateral lip of bicipital groove of humerus	Medial and lateral pectoral nerves from brachial plexus
Pectoralis minor	3rd, 4th, & 5th ribs	Coracoid process of scapula	Medial pectoral nerve from brachial plexus

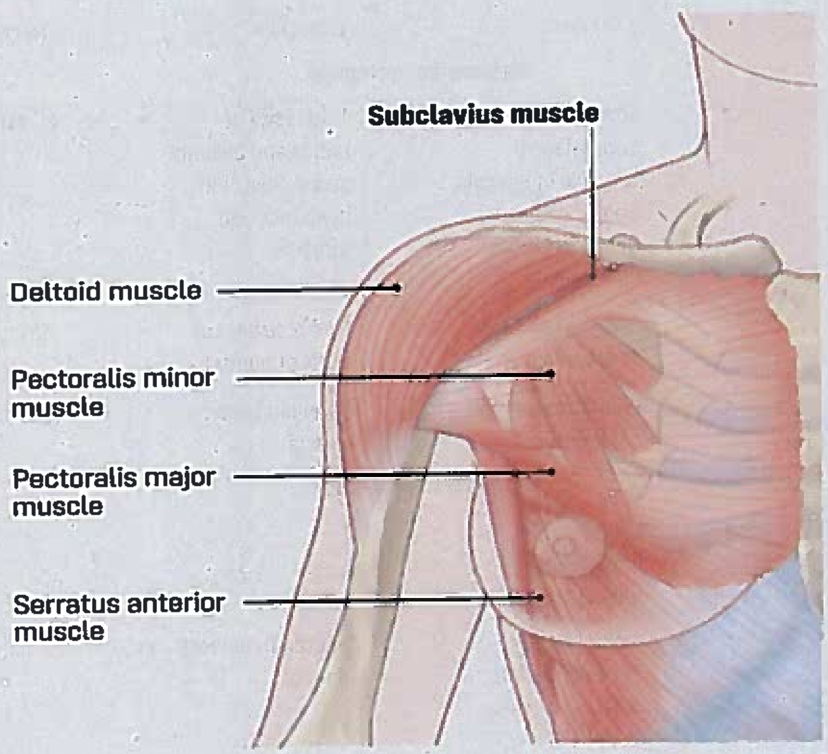
Subclavius	1st costal cartilage	Clavicle	Nerve to Subclavius
SubclaSerratus Anterior (Mnemonic: SALT)	Upper eight ribs	Medial border & inferior angle of scapula	Long Thoracic nerve

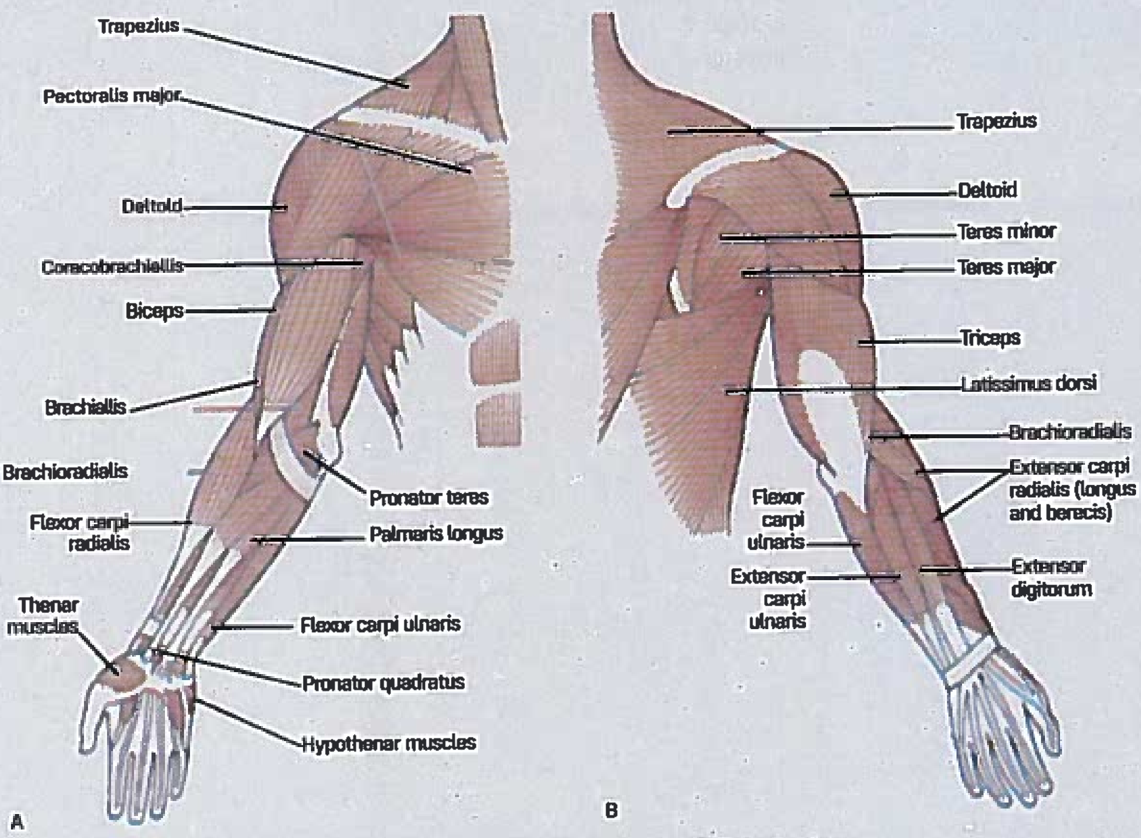
Muscles Connecting Upper Limb to Vertebral Column

Muscle	Origin	Insertion	Nerve Supply
Trapezius	• Occipital bone, • ligamentum nuchae, • C7 spine • T1- T12	• Upper fibers → lateral 3rd of clavicle • middle and lower fibers → acromion and spine of scapula	• Motor→Spinal part of accessory nerve • Sensory →C3 and C4
Latissimus dorsi	• Iliac crest, lumbar fascia • Spines of T7- T12 • Lower four ribs • Inferior angle of scapula	• Floor of bicipital groove of humerus	• Thoracodorsal nerve
Levator scapulae	• Transverse processes of C1 to C4	• Medial border of Scapula	• C3 and C4 nerve • Dorsal scapular nerve
Rhomboid minor	• Ligamentum nuchae and • Spines of C7 and T1	• Medial border of scapula	• Dorsal scapular nerve
Rhomboid major	• Spines of T2 – T5	• Medial border of scapula	• Dorsal scapular nerve

Muscles of Scapular Region (Connecting Scapula to Humerus)

Muscle	Origin	Insertion	Nerve Supply
Deltoid	Lateral third of clavicle, acromion, spine of scapula	Middle of lateral surface of shaft of humerus	Axillary nerve
Supraspinatous and Infraspinatous	Supraspinatous→Supraspinous fossa of scapula Infraspinatous →Infraspinous fossa of scapula	Greater tuberosity of humerus, capsule of shoulder joint	Suprascapular nerve
Teres minor	Upper 2/3rd of lateral border of scapula	Greater tuberosity of humerus; capsule of shoulder joint	Axillary nerve
Teres major	Lower 1/3rd of lateral border of scapula	Medial lip of bicipital groove of humerus	Lower subscapular Nerve
Subscapularis	Subscapular fossa	Lesser tuberosity of humerus	Upper and lower subscapular nerves

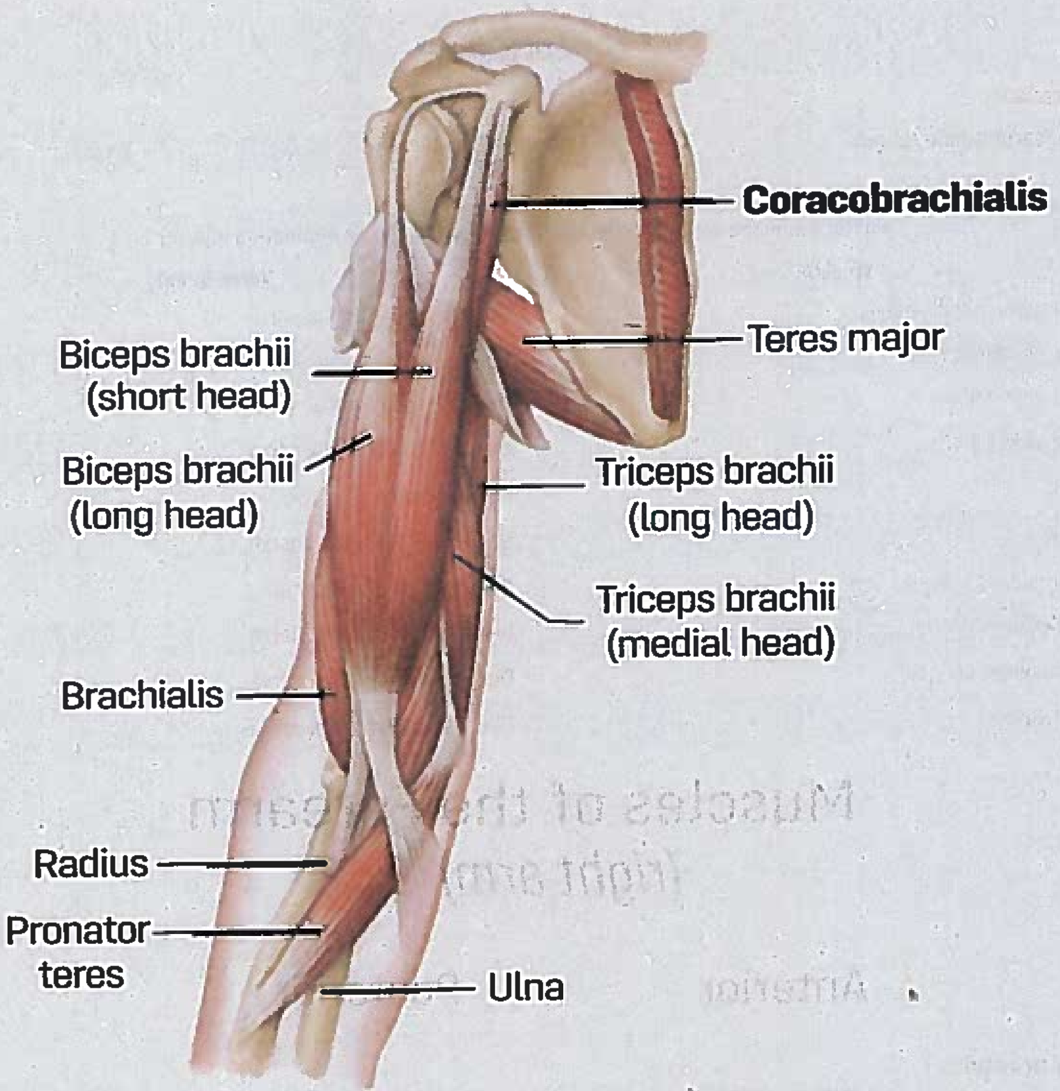




The main muscles of the shoulder and upper limb. A: anterior view. **B:** Posterior view.

Muscles of Upper Arm

Muscle	Origin	Insertion	Nerve Supply
Anterior Compartment			
Biceps brachii	• Long head→ Supraglenoid tubercle of scapula • Short head→ Coracoid process of scapula	• Tuberosity of radius and bicipital aponeurosis into deep fascia of forearm	• Musculocutaneous nerve
Coracobrachialis	• Coracoid process of scapula	• Medial aspect of shaft of humerus	• Musculocutaneous nerve
Brachialis	• Front of lower half of humerus	• Coronoid process of ulna	• Musculocutaneous nerve
Posterior Compartment			
Triceps	• Long head→ Infraglenoid tubercle of scapula • Lateral head →Upper half of posterior surface of shaft of humerus • Medial head Lower half of posterior surface of shaft of humerus	• Olecranon process of ulna	• Radial nerve



Muscles of Forearm

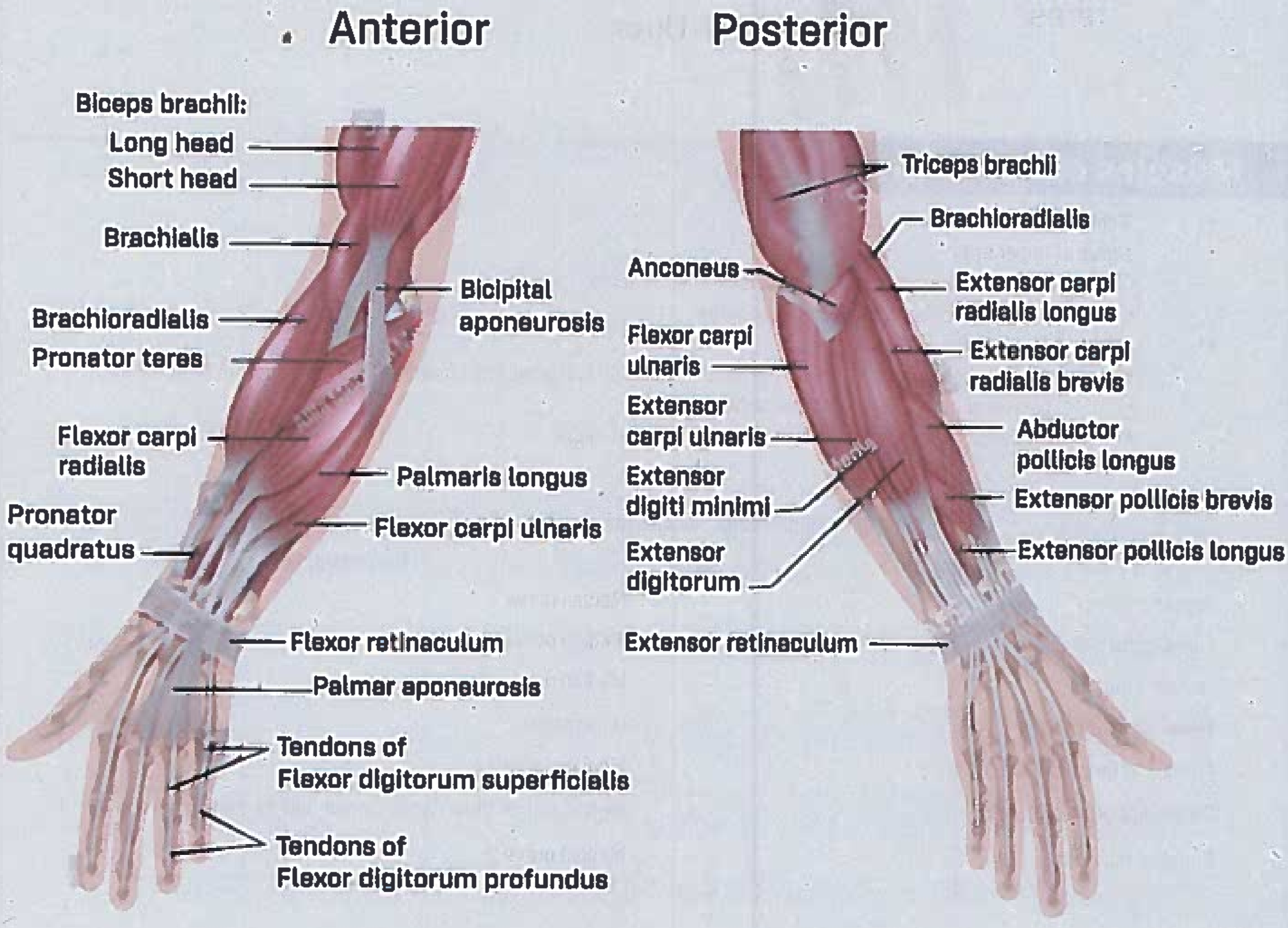
- Remember
- Nerve of upper arm
  - Anterior compartment → Musculocutaneous nerve
  - Posterior compartment → Radial nerve
- Nerve of forearm→
  - Anterior compartment → Median nerve (exception is flexor carpi ulnaris and flexor digitorum profundus)
  - Lateral compartment → Radial nerve
  - Posterior compartment → Deep branch of Radial nerve

Anterior compartment/flexors (pronators do pronation also)	
Muscle	**Nerve Supply**
Pronator Teres	Median nerve
Flexor carpi radialis	Median nerve
Palmaris longus	Median nerve
Flexor Carpi Ulnaris	Ulnar nerve
Flexor Digitorum Superficialis	Median nerve
Flexor digitorum profundus	Medial half → Ulnar while lateral half → median nerves
Pronator quadratus	Median nerve

Lateral compartment	
Brachioradialis	Radial nerve
Extensor carpi radialis longus	Radial nerve

Posterior compartment/ extensors (except supinator do supination of arm)	
Muscle	Nerve Supply
Extensor carpi radialis brevis	Deep branch of radial nerve
Extensor digitorum	Deep branch of radial nerve
Extensor digiti Minimi	Deep branch of radial nerve
Extensor carpi ulnaris	Deep branch of radial nerve
Anconeus	Radial nerve
Supinator	Deep branch of radial nerve
Abductor pollicis Longus	Deep branch of radial nerve
Extensor pollicis Brevis	Deep branch of radial nerve
Extensor pollicis Longus	Deep branch of radial nerve
Extensor indicis	Deep branch of radial nerve

Muscles of the Forearm
(right arm)



Small Muscles of the Hand

Muscle	Nerve Supply
Palmaris brevis	• Superficial branch of ulnar nerve
Lumbricals (4 in number)	• 1st and 2nd (i.e., lateral two)→median nerve • 3rd and 4th→deep branch of ulnar nerve
Interossei (8 in number , 4 out of which are palmar and 4 are dorsal)	• Deep branch of ulnar nerve

Short Muscles of Thumb

Muscle	Nerve Supply
Abductor pollicis brevis	• Median nerve
Flexor pollicis brevis	• Median nerve
Opponens Pollicis	• Median nerve
Adductor pollicis	• Deep branch of ulnar nerve

Remember mnemonic for median nerve in hand (MEat LOAF)

- MEat MEdian nerve
- 1ST AND 2ND LUMBRICALS
- Opponens Pollicis
- Abductor pollicis brevis
- Flexor pollicis brevis

Short Muscles of Little Finger

Muscle	Nerve Supply
Abductor digiti minimi	• Deep branch of ulnar nerve
Flexor digiti minimi	• Deep branch of ulnar nerve
Opponens digiti minimi	• Deep branch of ulnar nerve

Different Topics

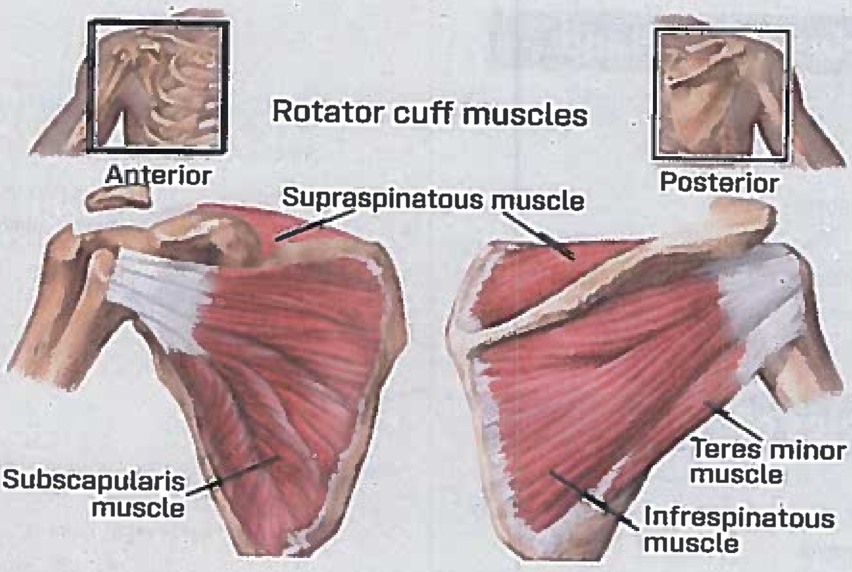
Quadrangular Space

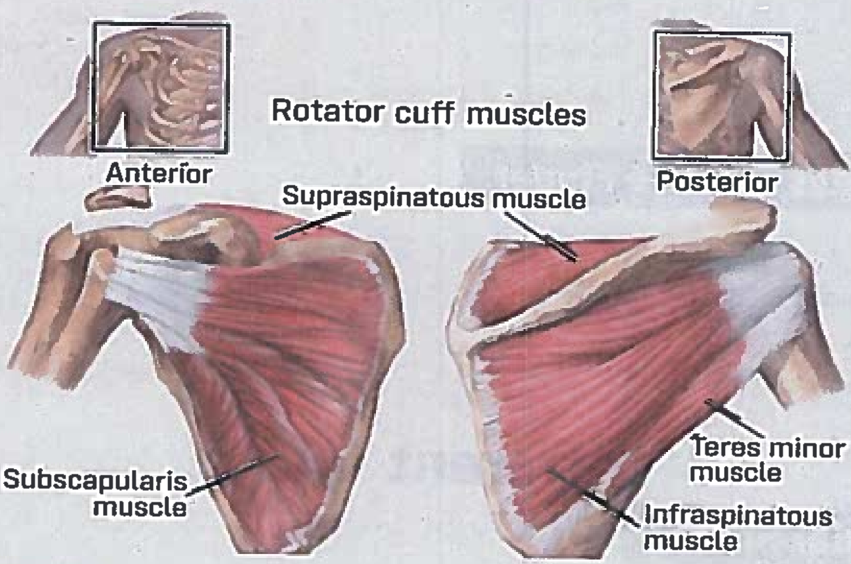
- Located immediately below the shoulder joint.
- Contents:
  - Axillary nerve, and Posterior circumflex humeral vessels.
- Boundaries

Superiorly	Inferiorly	Medially	Laterally
Subscapularis in front. Teres minor behind. Capsule of shoulder joint.	Teres major.	Long head of triceps	Surgical neck of humerus.

Rotator Cuff or Musculocutanoeous Cuff Of Shoulder

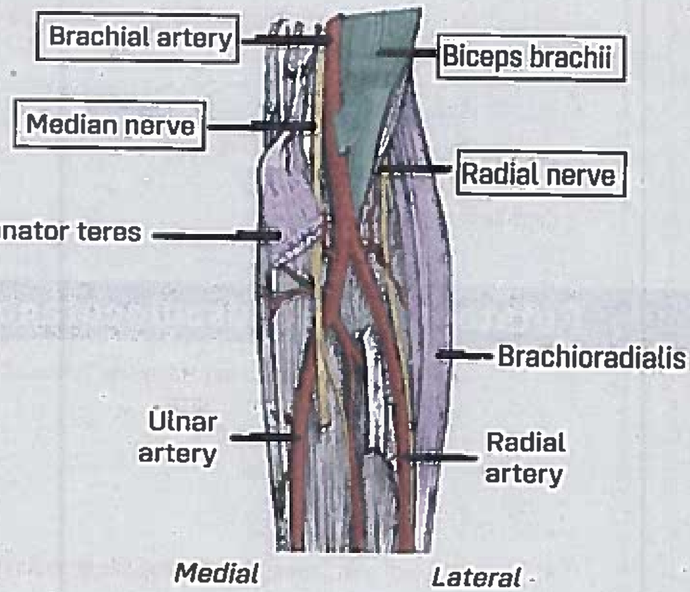
- This is a fibrous sheath formed by four flattened tendons which blend with the capsule of shoulder joint and strengthen it. (Mnemonic: **SITS**).
  - Supraspinatus.
  - Infraspinatous.
  - Teres minor.
  - Subscapularis.
- The cuff gives strength to the capsule all around except inferiorly.





Cubital Fossa

- Triangular hollow situated in front of the elbow.
- Boundaries:
  - Laterally: medial border of brachioradialis.
  - Medially: lateral border of pronator teres.
  - Base: directed upward, formed by imaginary line joining two epicondyles of humerus.
  - Apex: directed downward, formed by meeting point of lateral and medial boundaries.
- Contents: (From medial to lateral)—(MBBRS)
  - Median nerve
  - Bifurcation of brachial artery into ulnar and radial arteries.
  - Bicep muscle tendon
  - Radial nerve.
  - Superficially cephalic vein and basilic vein



Breast or Mammary Gland

Type	• Modified sebaceous gland.
Location	• Vertically: 2nd to 6th rib. • Horizontally: lateral border of sternum to mid axillary line

Deep relations	• Pectoralis major.
	• Pectoralis fascia
	• Retromammary space:
	    • Breast is separated from pectoral fascia by loose areolar tissue known as Retromammary space.
	    • Breast can move freely over pectoralis major due to this space

Structure of the breast	• Nipple
	    • Conical projection.
	    • At level of 4th intercostal space.
	    • Pierced by 15-20 lactiferous ducts
	• Parenchyma:
	    • Glandular tissue secretes milk
	    • Consists of 15 to 20 lobes.
	    • Each lobe is cluster of alveoli and is drained by lactiferous ducts.
	    • Lactiferous ducts pierces the nipple (lactiferous sinusampulla).
	• Stroma:
	    • Forms the supporting frame work of gland.
	    • Partly fibrous and partly fatty.
	        • Fibrous stroma: forms septa known as suspensory ligaments of cooper.
	        • Fatty stroma: forms the main bulk of the gland

Arterial supply	• Internal thoracic artery (branch of subclavian artery) • Lateral thoracic artery (branch of axillary artery) • Intercostal arteries
Venous drainage	• Internal thoracic vein, axillary vein
Nerve supply	• 4th to 6th intercostal nerve. • Nerves do not control the secretion of milk • Secretion controlled by prolactin.
Lymphatic drainage	• Axillary lymph nodes. • Internal mammary nodes. • Intercostal nodes. • Supraclavicular nodes.

Carpal Tunnel Syndrome

- This syndrome consists of sensory and motor symptoms in the hand caused by compression of median nerve in carpal tunnel.
- May be caused by

Bony pathology	**Soft tissue pathology**
• Arthritis of wrist and carpal joints. • Dislocation of lunate or old fracture of wrist.	• Tenosynovitis. • Acromegaly • Myxoedema. • Toxaemia of pregnancy.

Flexor Retinaculum

This is a strong fibrous band which bridges the anterior concavity of the carpus and converts it into a tunnel, the carpal flexor tunnel.

- Attachment's

Medially	Laterally
• Pisiform bone. • Hook of the hamate.	• Tubercle of scaphoid. • Crest of trapezium.

- Structures passing

Structures passing superficial to the flexor retinaculum	Structures passing deep to the flexor retinaculum (Medical Superintendent is FuLLy Boring)
• Tendon of palmaris longus. • Palmar cutaneous branch of median nerve and ulnar nerve • Ulnar vessels and ulnar nerve.	• Median nerve • Tendons of flexor digitorum Superficialis. • Tendon of Flexor polLicis longus. • Bursa → Ulnar and radial

Extensor Retinaculum

- The deep fascia on the back of wrist is thickened to form extensor tendon in place.
- Attachment

Medially	Laterally
• Styloid process of ulna • Triquetral • Pisiform bone	• To lower part of anterior border of radius.

Thenar eminence

Thenar eminence	Hypothenar eminence
Formed by short muscles of thumb • Abductor pollicis brevis • Flexor pollicis brevis • Opponens pollicis.	Formed by short muscles of finger • Abductor digiti minimi • Flexor digiti minimi • Opponens digiti minimi.

Clavipectoral Fascia

Attachments	• Above → clavicle while Below→ axillary fascia • Medially → first rib and costoclavicular ligament • Laterally→ coracoid process blends with coracoclavicular ligament

Contents	• Encloses:
	  • Subclavius muscle & Pectoralis minor muscle.
	• Pierced by: (TLC)
	  • Thoracoacromial vessels, Lateral pectoral nerve, Lymph vessels & Cephalic vein.

Radial Groove: (Spiral Groove)

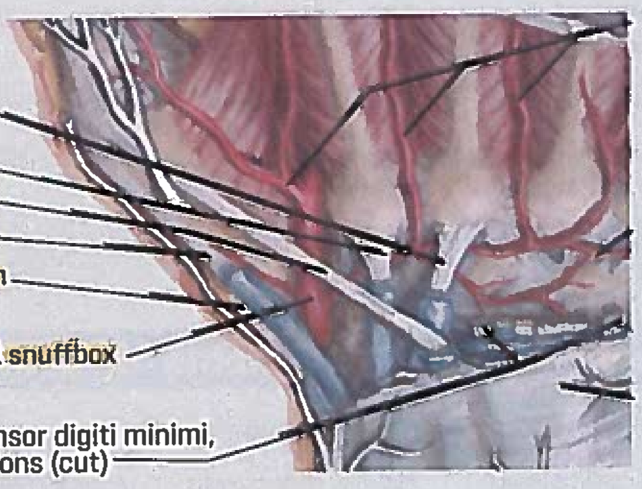
- Present on the upper part of anterolateral surface of shaft of humerus.
- Contents →Radial nerve and Profunda brachii vessels.

Bicipital Groove: (Intertubercular Sulcus)

- Present between greater and lesser tubercle of the humerus.
- Contents →Tendon of long head of biceps and Ascending branch of ant. Circumflex humeral artery.

Anatomical Snuffbox

- Triangular depression on lateral side of the wrist.
- Boundaries:
  - Anteriorly: tendon of abductor pollicis longus and extensor pollicis brevis
  - Posteriorly: tendon of extensor pollicis longus
- Contents:
  - Radial artery and Scaphoid bone



Compartment Syndrome

- Compartment syndrome occurs when the tissue pressure within a closed muscle compartment exceeds the perfusion pressure and results in muscle and nerve ischemia.
- Clinical features include
  - Pain
  - Paraesthesia (altered sensation e.g., "pins & needles") in the cutaneous nerves of the affected compartment is another typical sign.
  - Paralysis of the limb (is usually a late finding)
  - Congestion of the digits with prolonged capillary refill time.

Muscles Producing Movements of Upper Limb

Muscles Producing Movements of Shoulder Joint

Flexors of shoulder	Extensors of shoulder joint	Abductors of shoulder joint	Adductors of shoulder joint	Lateral rotators of shoulder joint	Medial rotators of shoulder joint
Anterior fibers of deltoid.	Posterior fibers of deltoid.	Supraspinatous muscle.	Pectoralis major.	Infraspinatous	Subscapularis
Pectoralis major	Latissimus dorsi	Middle fibers of deltoid.	Latissimus dorsi	Teres minor	Latissimus dorsi
Biceps brachii	Teres major.	Triceps (overhead abduction).	Teres major and minor	Posterior fibers of deltoid	Teres major
Coracobrachialis					

Muscles Producing Movements of Forearm

Flexors of forearm (at elbow joint) (3 B's bend the elbow)	Extensor of forearm (at elbow joint)	Pronator of forearm (At superior and inferior radioulnar joint)	Supinator of forearm (At superior and inferior radioulnar joint)
Brachialis Biceps brachii Brachioradialis	Triceps Anconeus	Pronator teres Pronator quadratus Flexor carpi radialis Palmaris longus	Biceps brachii (chief) Supinator.

Movements of Wrist Joint

Flexors of wrist joint	Extensors of wrist joint	Abductors of wrist joint	Adductors of wrist joint
Flexor carpi radialis and flexor carpi ulnaris	Extensor carpi radialis (longus + brevis)	Flexor and extensor carpi radialis	Flexor and extensor carpi ulnaris.
Palmaris longus	Extensor carpi ulnaris.	Abductor pollicis longus	Flexor and extensor carpi ulnaris.
Flexor digitorum superficialis (assisted)	Extensor digitorum (assisted)	Extensor pollicis longus	
Flexor pollicis longus (assisted)	Extensor digiti minimi (assisted)		

Muscle Producing Movements of Thumb

Extension	Abduction	Adduction	Opposition
Extensor pollicis longus Extensor pollicis brevis.	Abductor pollicis longus Abductor pollicis brevis	Adductor pollicis	Opponens pollicis.

Muscles Producing Movements of Fingers

- Dorsal interossei ABduction (D-AB)
- Palmar interossei ADduction (P-AD).
- Flexion and extension by: lumbricals and interossei.

Axillary Artery

- Continuation of subclavian artery.
- Extends from outer border of first rib to lower border of teres major muscle.
- It continues as brachial artery.
- The pectoralis minor muscle crosses it and divides into three parts.
  - 1st part: Superior to muscle
  - 2nd part: Posterior to muscle
  - 3rd part: Inferior to muscle
- Branches (Screw The Lawyer Save A Patient)

1st part	2nd part	3rd part
Superior thoracic artery.	Thoracoacromial Lateral thoracic artery	Subscapular artery. Anterior circumflex humeral artery Posterior circumflex humeral artery

Brachial Artery

- Continuation of axillary artery
- Extends from lower border of teres major muscle
- Terminate at neck of radius by dividing into radial and ulnar artery.
- Branches:
    - Muscular branches
    - Nutrient artery to humerus
    - Profunda brachii artery: large branch that follows radial nerve in posterior compartment
    - Superior ulnar collateral artery
    - Inferior ulnar collateral artery.
    - Terminal branches: radial and ulnar artery.

Radial Artery

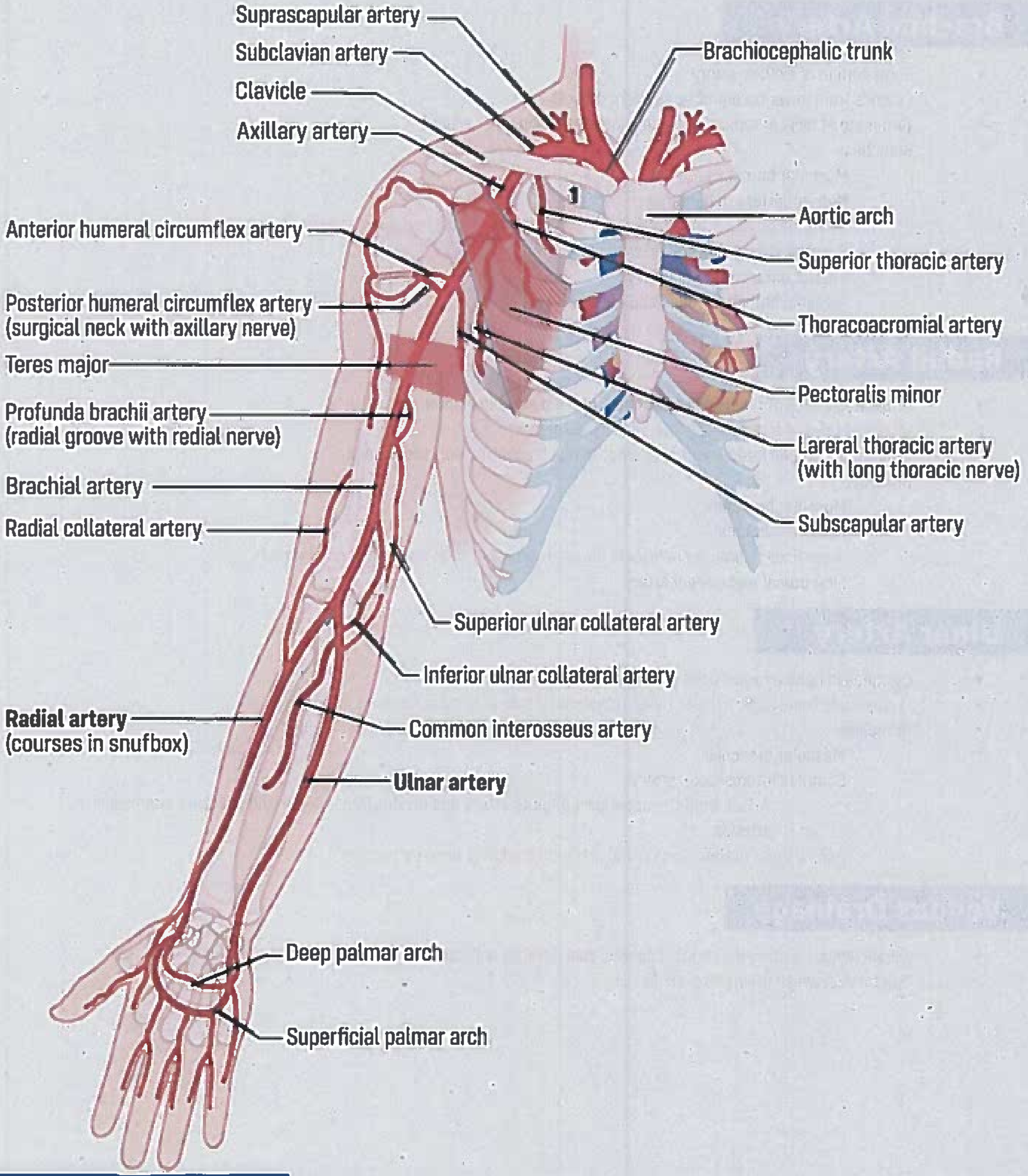
- Originate at neck of radius and terminates at hand as deep palmar arch.
- In middle third of forearm radial nerve lies lateral to it.
- Winds back around lateral aspect of wrist to reach posterior surface of hand.
- Branches:
    - Muscular branches
    - Recurrent branch:
    - Superficial palmar branch: joins the ulnar artery to form superficial palmar arch
    - First dorsal metacarpal artery

Ulnar Artery

- Continue in hand as superficial palmar arch
- It enters the hand superficial to flexor retinaculum lateral to ulnar nerve
- Branches:
    - Muscular branches
    - Common interosseous artery:
        - Arises from the upper part of ulnar artery and divides into anterior and posterior interosseous arteries.
    - Deep palmar branch: joins radial artery to complete deep palmar arch

Venous Drainage

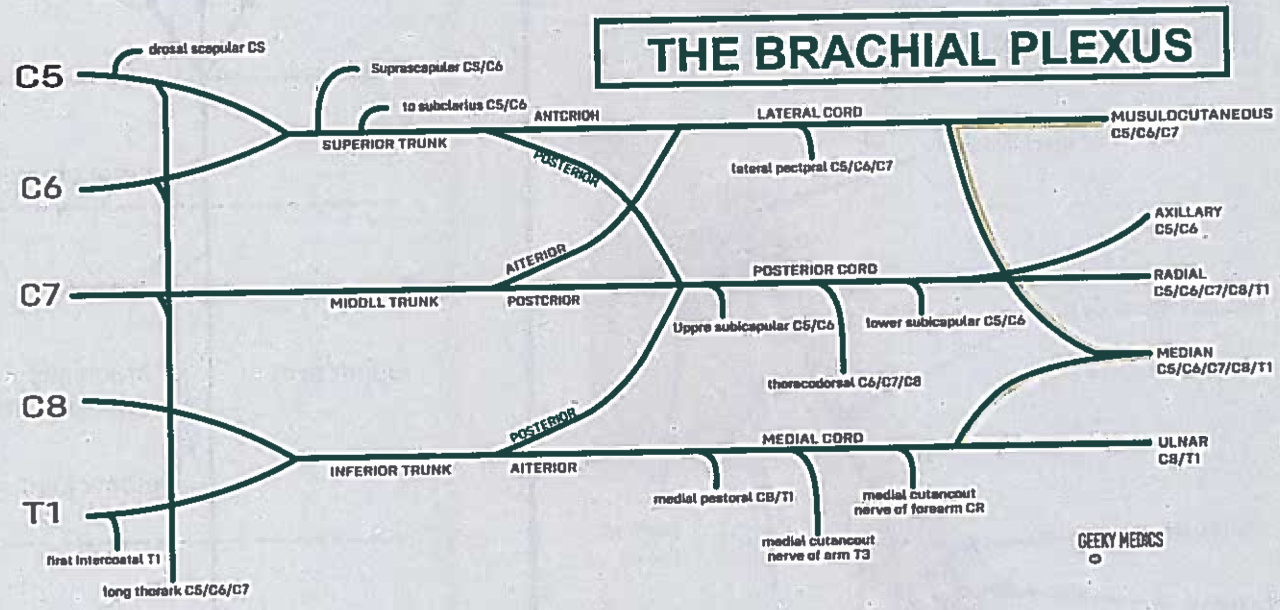
- Dorsal venous arch → divide into cephalic vein (lateral) and basilic vein (medial) → from cephalic vein median cubital vein which drains into basilic vein



Brachial Plexus

Roots	• Anterior primary rami of spinal nerves C5, 6, 7, 8 and T1. ◦ Prefixed plexus: contribution by c4 is large and T2 is often absent ◦ Postfixed plexus: lacks C5 but has T2 contribution
Trunks	• Superior trunk: C5 and C6 • Middle trunk: C7 • Inferior trunk: C8 and T1. • Divisions of trunk Each trunk divides into ◦ Anterior or ventral division ◦ Posterior or dorsal division

Cords	• Lateral cord: Union of anterior division of upper and middle trunk • Medial cord: Anterior division of lower trunk • Posterior cord: Union of posterior divisions of all three trunks.



Branches of Brachial Plexus

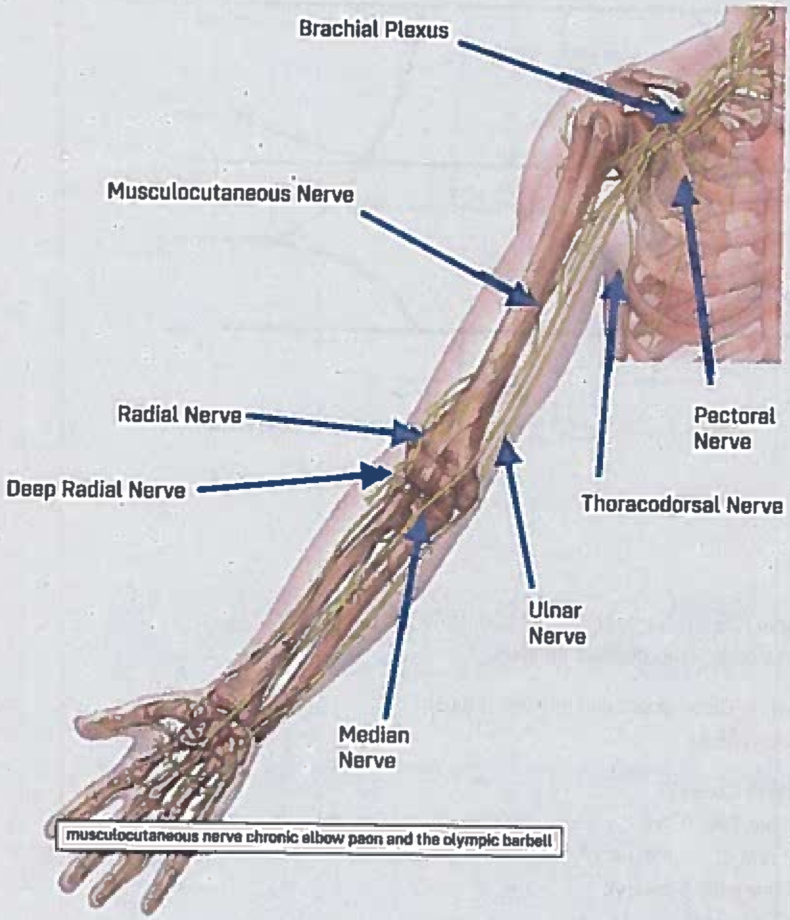
Branches of root	• Long thoracic nerve (C5,6,7- nerve to serratous anterior) • Dorsal scapular nerve (c5- rhomboidus muscle)
Branches of trunk (Only from upper trunk)	• Suprascapular nerve (C5,6—supra and infraspinatous) • Nerve to Subclavius (C5.6).

Branches of cords	• Lateral cord: (**2LM**) (C5,6,7)
	  ◦ **L**ateral pectoral nerve
	  ◦ **L**ateral root of median nerve
	  ◦ **Musculocutanoeous nerve**
	• Medial cord: (**4MU**) (C8,T1)
	  ◦ **M**edial pectoral nerve.
	  ◦ **M**edial cutaneous nerve of arm
	  ◦ **M**edial cutaneous nerve of forearm
	  ◦ **M**edial root of median nerve
	  ◦ **U**lnar nerve.
	• Posterior cord: (**2STAR**)
	  ◦ Upper**S**ubscapular (c5,6)
	  ◦ Lower**S**ubscapular (c5,6)
	  ◦ **T**horacodorsal nerve (c6, 7, 8- nerve to Latissimus dorsi).
	  ◦ **A**xillary nerve (c5,6)
	  ◦ **R**adial nerve (c5, 6, 7, 8, T1).

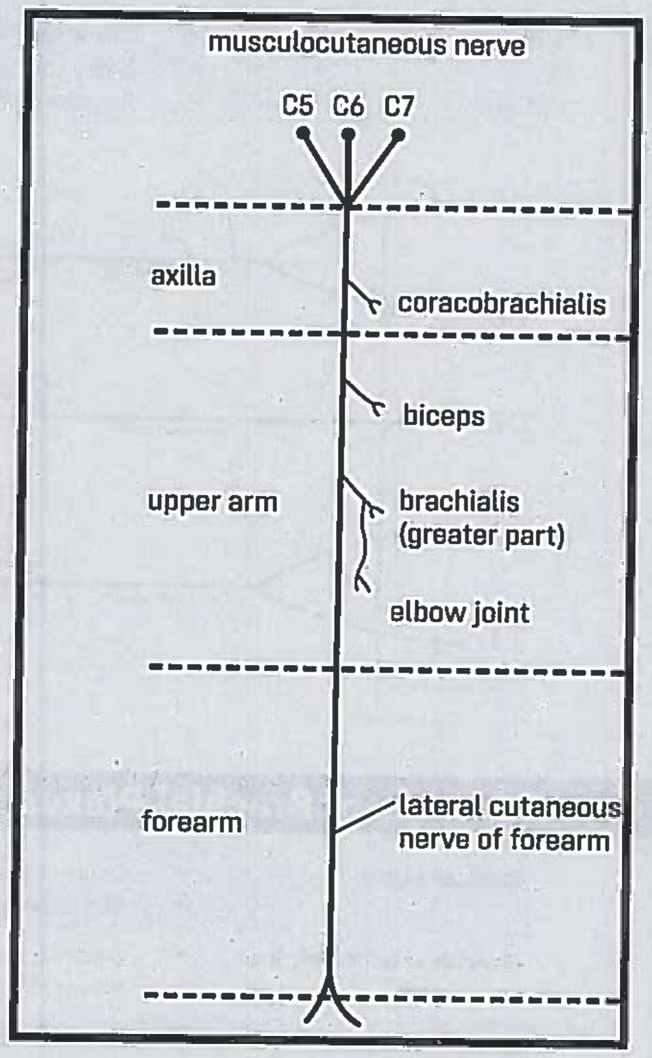
Musculocutanoeous Nerve

- C5,6,7
- Called musculocutanoeous because muscular in arm and cutaneous in forearm.
- In lower part of axilla accompanies axillary artery (lies lateral to artery)
- Leaves the axilla and enters the front of arm by piercing Coracobrachialis.
- Passes downward between biceps and brachialis.
- Appears at lateral margin of bicep tendon.
- Pierces deep fascia and continue down in forearm as lateral cutaneous nerve of forearm.

Muscular **(BBC)**	**B**iceps **B**rachialis **C**oracobrachialis
Cutaneous	Lateral cutaneous nerve of forearm.
Articular branch	Elbow joint

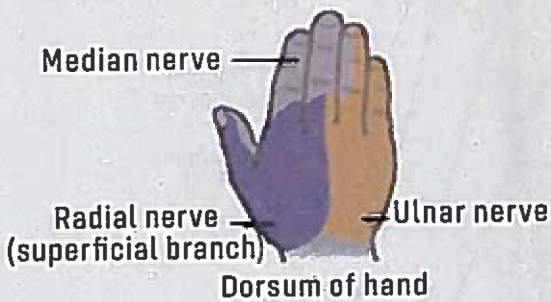


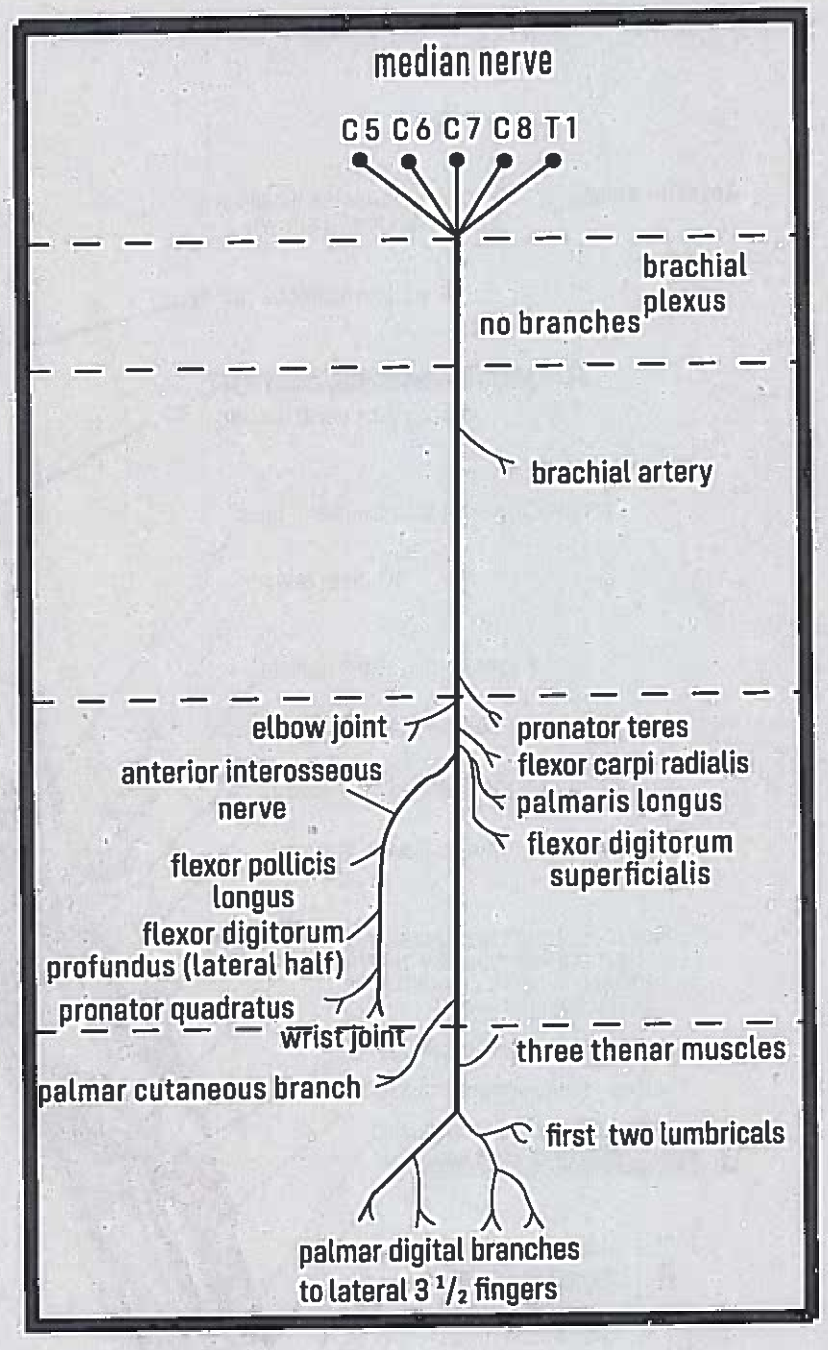
musculocutaneous nerve chronic elbow paon and the olympic barbell



Median Nerve

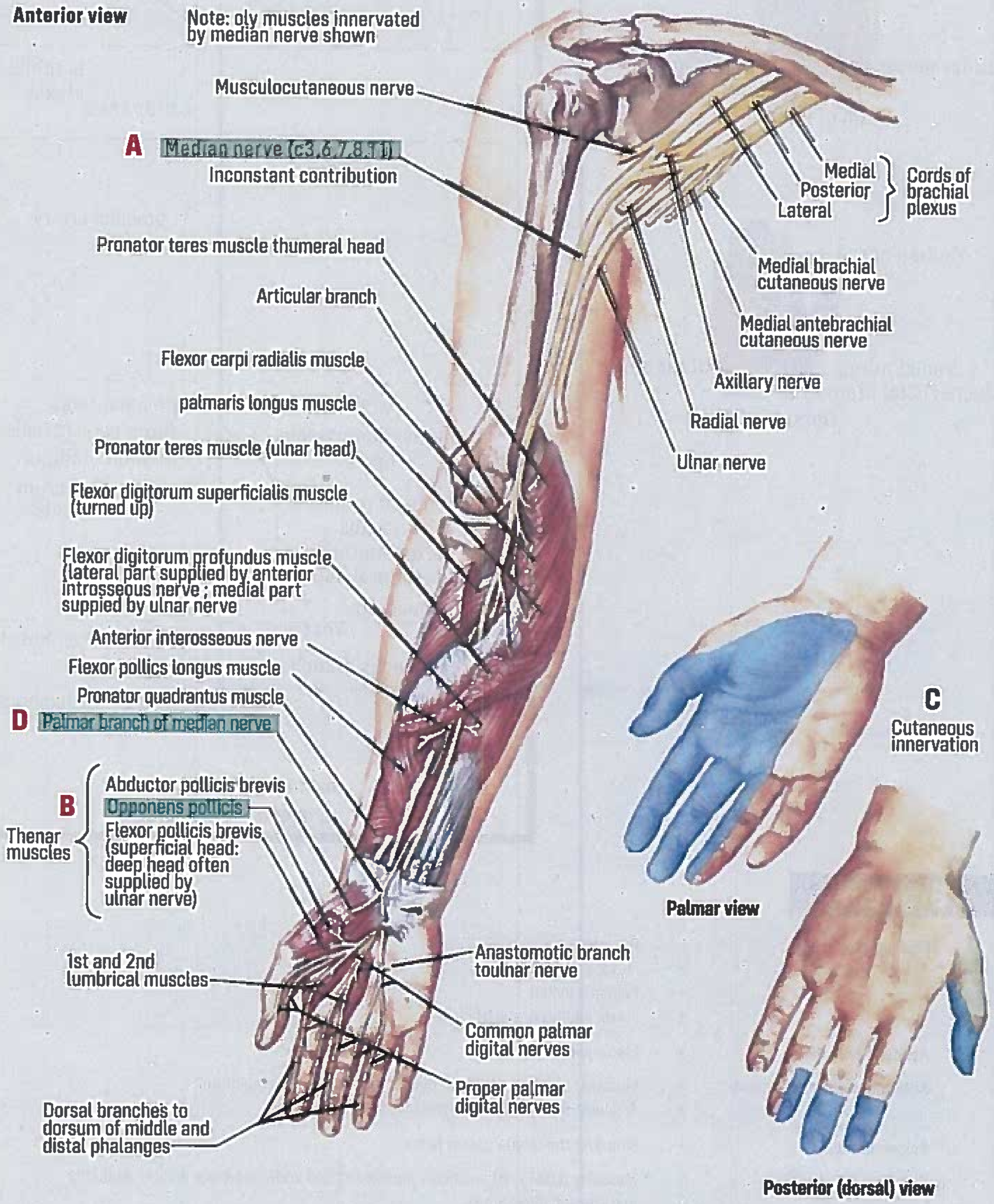
- Arises from lateral and medial cord of brachial plexus (C5, C6, C7, C8, and T1).
- It descend on lateral side of axillary and brachial artery.
- Halfway down the arm it crosses the brachial artery to reach its medial side.
- The nerve then descends through the forearm between the two heads of pronator teres (anterior interosseous nerve).
- Runs on posterior surface of flexor digitorum superficialis.
- At wrist it lies behind the tendon of palmaris longus.
- The median nerve enters the palm by passing behind the flexor retinaculum and through the carpal tunnel.





Branches

Muscular branches	• Pronator teres • Flexor carpi radialis. • Palmaris longus • Flexor digitorum superficialis
Articular branches:	• Elbow joint
Anterior interosseous nerve	• Muscular branches→ flexor pollicis longus, pronator quadratus • Articular→ to wrist and carpal joints
Palmar branch	• Skin over the lateral part of palm
Branches in palm	• Muscular (LOAF) →Lumbricals muscle (1st and 2nd), Opponens pollicis, Abductor and Flexor pollicis brevis, , • Cutaneous→palmar aspect of lateral 3 and half fingers and distal half of dorsal aspect of each finger as well.



Anterior view
Note: oly muscles innervated by median nerve shown
Musculocutaneous nerve
A
Median nerve (c3,6,7,8,T1)
Inconstant contribution
Pronator teres muscle thumeral head
Articular branch
Flexor carpi radialis muscle
palmaris longus muscle
Pronator teres muscle (ulnar head)
Flexor digitorum superficialis muscle (turned up)
Flexor digitorum profundus muscle (lateral part supplied by anterior introsseous nerve ; medial part suppied by ulnar nerve
Anterior interosseous nerve
Flexor pollics longus muscle
Pronator quadrantus muscle
D
Palmar branch of median nerve
B
Thenar muscles
Abductor pollicis brevis
Opponens pollicis
Flexor pollicis brevis (superficial head: deep head often supplied by ulnar nerve)
1st and 2nd lumbrical muscles
Dorsal branches to dorsum of middle and distal phalanges
Medial
Posterior
Lateral
Cords of brachial plexus
Medial brachial cutaneous nerve
Medial antebrachial cutaneous nerve
Axillary nerve
Radial nerve
Ulnar nerve
Anastomotic branch toulnar nerve
Common palmar digital nerves
Proper palmar digital nerves
C
Cutaneous innervation
Palmar view
Posterior (dorsal) view

Ulnar Nerve and Radial Nerve

Ulnar nerve	Radial nerve
• Arises from medial cord of brachial plexus C8, T1	• Arises from posterior cord of brachial plexus C5, C6, C7, C8, T1.
• It descend along medial side of axillary and brachial arteries upto insertion of Coracobrachialis	• Winds around spiral groove of humerus along with profunda brachii artery.
• Then pierces medial intermuscular septum and enters posterior compartment of arm	• Enters posterior compartment of arm
• It then passes behind the medial epicondyle of humerus, enters forearm, passes anterior to flexor retinaculum.	• It descends in front of lateral epicondyle and
• Divides into superficial and deep terminal branches	• Divides into superficial and deep branches.

• Branches:
• Muscular:
  • Flexor carpi ulnaris
  • Medial half of flexor digitorum profundus
• Articular:
  • Elbow joint
• Dorsal cutaneous branch:
  • Supplies skin over medial side of the back of hand.
  • Medial one and half fingers over proximal phalanges.
• (Rest in figure)
	• Branches:
	  • In axilla: triceps
	  • In middle arm: triceps and anconeus
	  • In front of lateral epicondyle: brachialis, brachioradialis, extensor carpi radialis longus.
	  • Superficial branch of radial nerve:
	  • Deep branch of radial nerve (posterior interosseous nerve):
	• Rest in figure

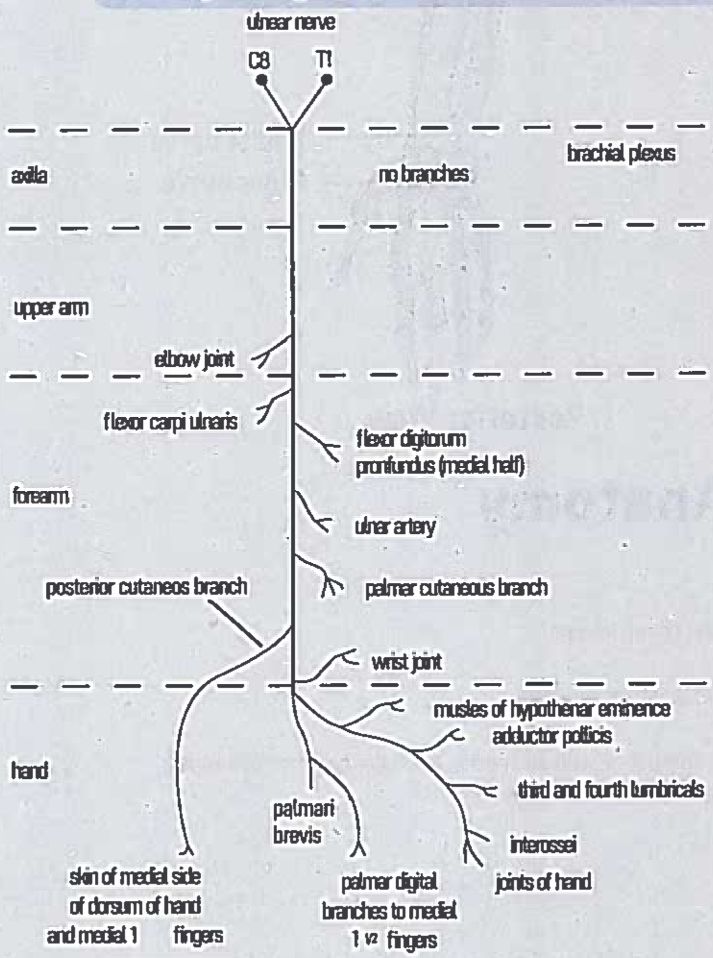


FIGURE 9.23 Summary of the main branches of the ulnar nerve.

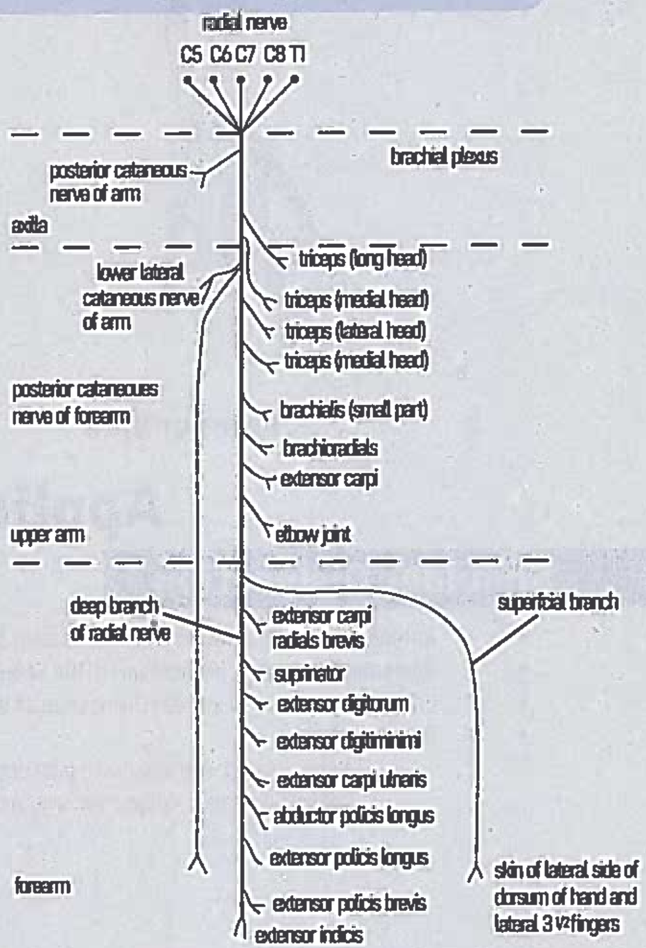
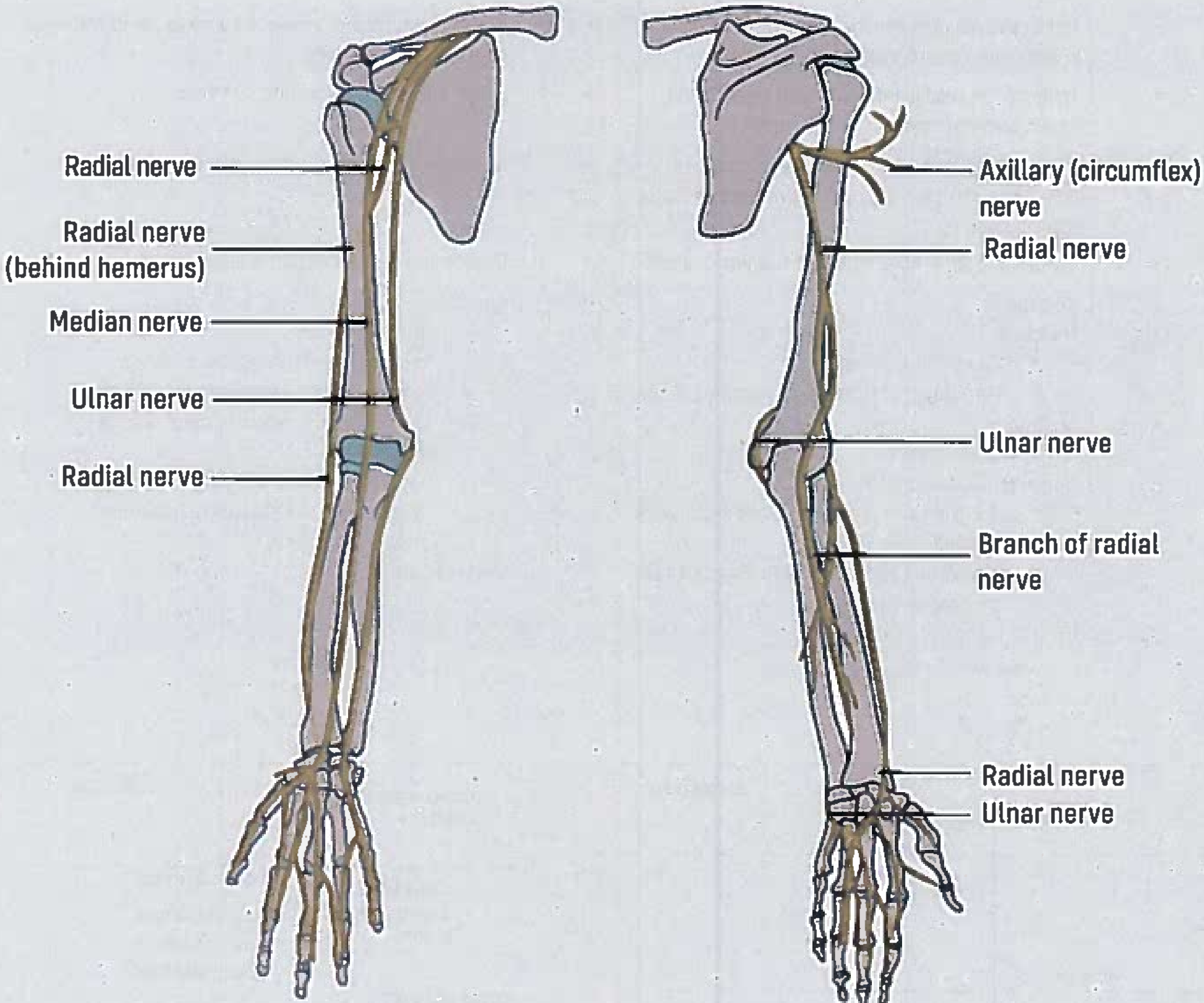


FIGURE 9.25 Summary of the main branches of the radial nerve.

Axillary Nerve

- C5, C6
- Passes through quadrangular space below shoulder joint with circumflex humeral vessels.
- Supplies shoulder joint, deltoid muscle



Anterior View

Posterior View

Applied Anatomy

Shoulder Dislocation

- Anterior (Front) Dislocation Of The Shoulder Joint → most common type
- Posterior (Backward) Dislocation Of The Shoulder Joint
- Inferior (downward to armpit) Dislocation of the Shoulder Joint → very rare
- Complications:
  - Nerve injured: Axillary nerve (can occur in both anterior as well as inferior, but more common in inferior)
  - Vessels damage: Axillary vessels (more common in anterior dislocation)

Arm abduction

Range of movements	Muscle	Nerve	
Upto 15°	Supraspinatus	Suprascapular	
15-90°	Deltoid	Axillary	
Beyond 90°	Serratous anterior	Long thoracic	
	Trapezius	Accessory	A person cannot comb his hair if accessory nerve damaged

Nerve injury

- The accessory nerve can be injured as the result of stab wounds to the neck.
- The axillary nerve can be injured in dislocations of the shoulder joint.

Dupuytren's Contracture

- Dupuytren's contracture is a localized thickening and contracture of the palmar aponeurosis

Fractures

- Bennett's fracture→Oblique fracture of base of metacarpal of thumb.
- Colle's fracture →Fracture of radius 2 centimetre above lower end of radius, Due to fall on outstretched hand
- Smith's fracture →Fracture of distal radius due to fall on back of hand.

Brachial Plexus Injuries

Injury to Upper Trunk	• Upper trunk→Erb's paralysis
	• Causes: Undue separation of head from shoulder as seen in
	  ◦ Birth injury
	  ◦ Fall on shoulder
	  ◦ During anaesthesia.
	• Deformity:
	  ◦ Arm hangs by the side
	  ◦ It is adducted and medially rotated, extended and pronated (waiters tip hand).

Injury to Lower Trunk	• Lower trunk → klumpke's paralysis.
	• Causes: Undue abduction of arm as in
	  ◦ Clutching
	  ◦ Fall from a height.
	• Deformity:
	  ◦ Claw hand.
	  ◦ Horner's syndrome

Injury of Long Thoracic Nerve	• It is Nerve to serratous anterior:
	• Causes:
	  ◦ Sudden pressure on the shoulder from above
	  ◦ Carrying heavy loads on shoulder.
	• Deformity:
	  ◦ Winging of scapula that is excessive prominence of the medial border of scapula (normally pull of muscle keeps medial border against thoracic wall)
	• Results in:
	  ◦ Loss of pushing and punching action.
	  ◦ Arm cannot be raised above 90 degree. That is over head.

Injury of Radial Nerve	• Causes:
	  ◦ Fracture of midshaft of humerus (spiral groove)
	• Deformity:
	  ◦ Wrist drop
	  ◦ Unable to extend wrist and fingers

Injury to Median Nerve	• Control coarse movement of hand therefore called labourers nerve.
	• Ape thumb deformity:
	  ◦ Due to paralysis of thenar muscles
	  ◦ Thumb adducted and laterally rotated.
	  ◦ Opposition of thumb completely lost.
	  ◦ Unable to pick up a pen with thumb and index finger.

Injury to Ulnar Nerve	• Called musicians nerve because control fine movements of fingers.
	• Deformity:
	  ◦ Claw hand
	  ◦ Flexion of terminal phalanges of ring and little finger is lost.

Mnemonic **DR. CUMA**	• **D** rop wrist ----------**R** adial nerve • **C** lawhand -----------**U** lnar nerve • **M** edian nerve ------**A** pe hand

Blood supply of Humerus

- Blood supply of head of humerus → Arcuate > anterior circumflex
- Blood supply of neck of humerus → Anterior and posterior circumflex

Bicipital Groove

- Attachments of muscles near it ("The **LADY** between **TWO MAJORS**")
  - Teres **MAJOR** attaches to medial lip of groove.
  - Pectoralis **MAJOR** to lateral lip of groove.
  - **LAT** issimus (Lady) is on floor of groove, between the 2 majors.

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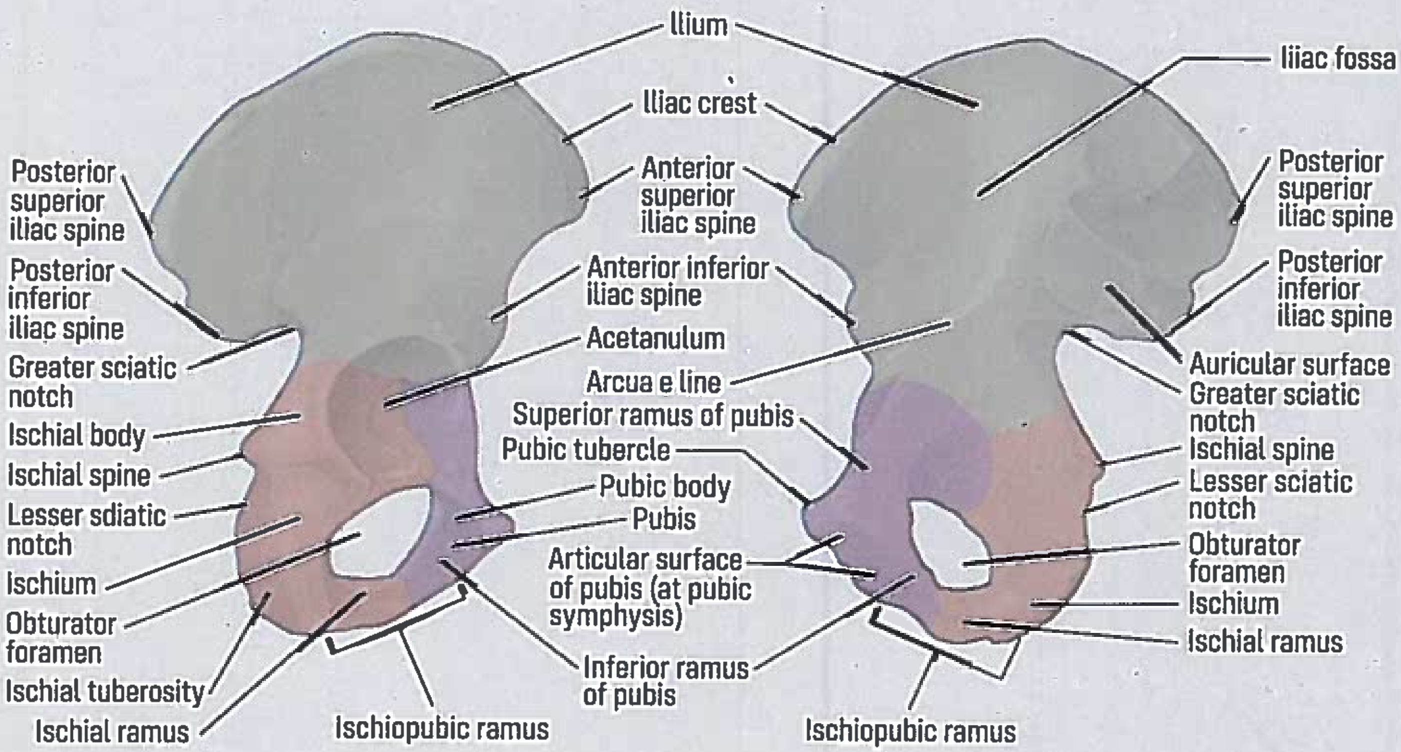
Chapter 2: Lower Limb

BONES OF LOWER LIMB

- The pelvic girdle consists of four bone, the two hip bones, the sacrum, and the coccyx.

Hip Bone

- Each hip bone consists of ilium, the ischium and the pubis.
- The acetabulum is a cup shaped depression, on the outer surface of the hip bone and articulates with the head of femur.
- The acetabular fossa is the floor of the acetabulum which is non articular.
- The acetabular notch is situated on the inferior margin of the acetabulum.
- The iliac crest runs between the anterior and posterior superior iliac spine.
- Below these spines are the corresponding inferior iliac spines.
- The ischium possesses an ischial spine and an ischial tuberosity.
- The body of pubis has pubic crest and pubic tubercle and it articulates with the pubic bone of opposite side at the symphysis pubis.
- The obturator foramen is a large opening that is bounded by the parts of the ischium and pubis.



Lateral view, right hip bone

Medial view, right hip bone

Femur

- Head of femur is hemispherical in shape and fits into the acetabulum to form hip joint.
- The fovea capitis is a small depression in the center of head for the attachment of ligament of head.
- Below head is neck and below neck are large eminences that are greater and lesser trochanters.
- Connecting the two trochanters are intertrochanteric line anteriorly (site of illiofemoral ligament attachment) and a prominent intertrochanteric crest posteriorly (on which is the quadrate tubercle).
- The shaft is smooth anteriorly but has a ridge posteriorly (the linea aspera) to which are attached muscle and intermuscular septa.
- The medial margin of the linea aspera continues below as the medial supracondylar ridge to the adductor tubercle on medial condyle.
- The lateral margin becomes continuous below with lateral supracondylar ridge.
- On the posterior surface of shaft below the greater trochanter is gluteal tuberosity for insertion of gluteus maximus muscle.
- A flat triangular area on posterior surface of lower end of shaft is called popliteal surface.
- The lower end of femur has a lateral and a medial condyle which are separated posteriorly by intercondylar notch.
- The anterior surface of the condyles are joined by an articular surface for the patella.
- The two condyles takes part in formation of the knee joint.
- Above the condyles are the medial and lateral epicondyles.
- The adductor tubercle is continuous with the medial epicondyle.

Patella

- Triangular in shape, largest sesamoid bone (a bone that develops within a tendon).
- It lies within the tendon of the quadriceps femoris muscle in front of the knee joint.
- Apex lies inferiorly and is connected to the tuberosity of tibia by ligamentum patellae.
- The posterior surface articulates with the condyles of femur.

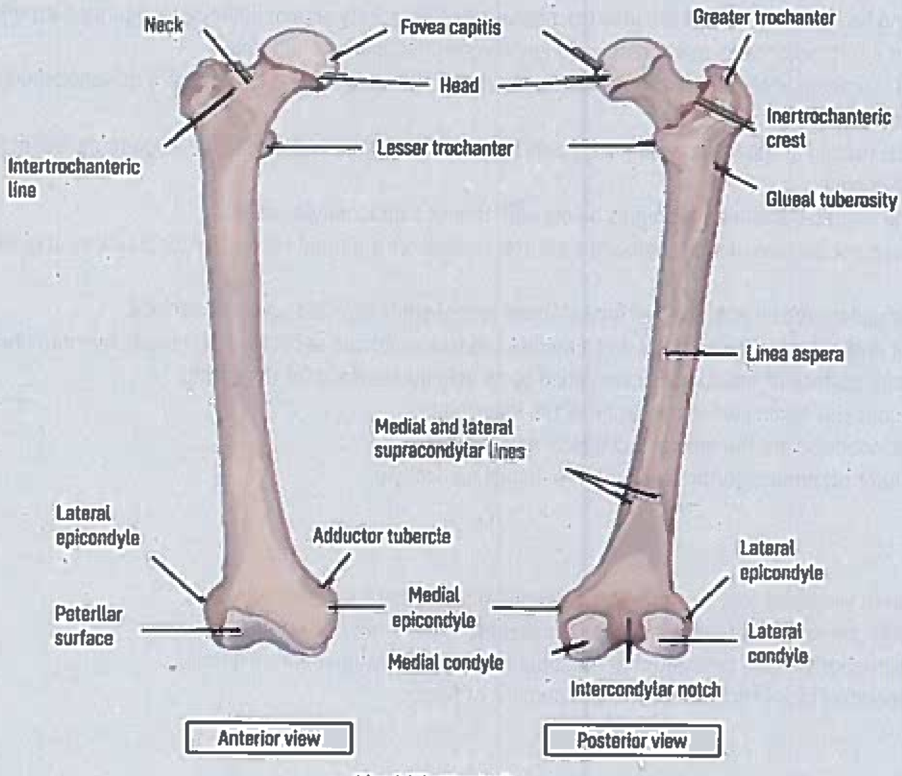
Tibia

- Medial bone of the leg. At upper end are lateral and medial condyles which articulate with condyles of femur.
- Separating the upper articular surface of tibial condyles is intercondylar eminence.
- The lateral condyle possesses an oval articular facet for the head of the fibula on its lateral aspect.
- At upper end of anterior border of shaft of tibia is tuberosity, which receives attachment of ligamentum patellae.
- The anterior border is prolonged downwards and medially to form the medial malleolus below.
- The lateral border of tibia provides attachment to interosseous membrane which binds tibia and fibula.
- The lower end of tibia shows a wide rough depression on its lateral surface for articulation with the fibula.

Fibula

- Provides attachment to muscle, no part in knee joint, but below forms a part of ankle joint.
- The head forms the upper end, it has a styloid process and articulation surface for articulation with the lateral condyle of tibia.
- The shaft is attached to the tibia by interosseous membrane.
- The lower end forms the lateral malleolus.

Femur Bone



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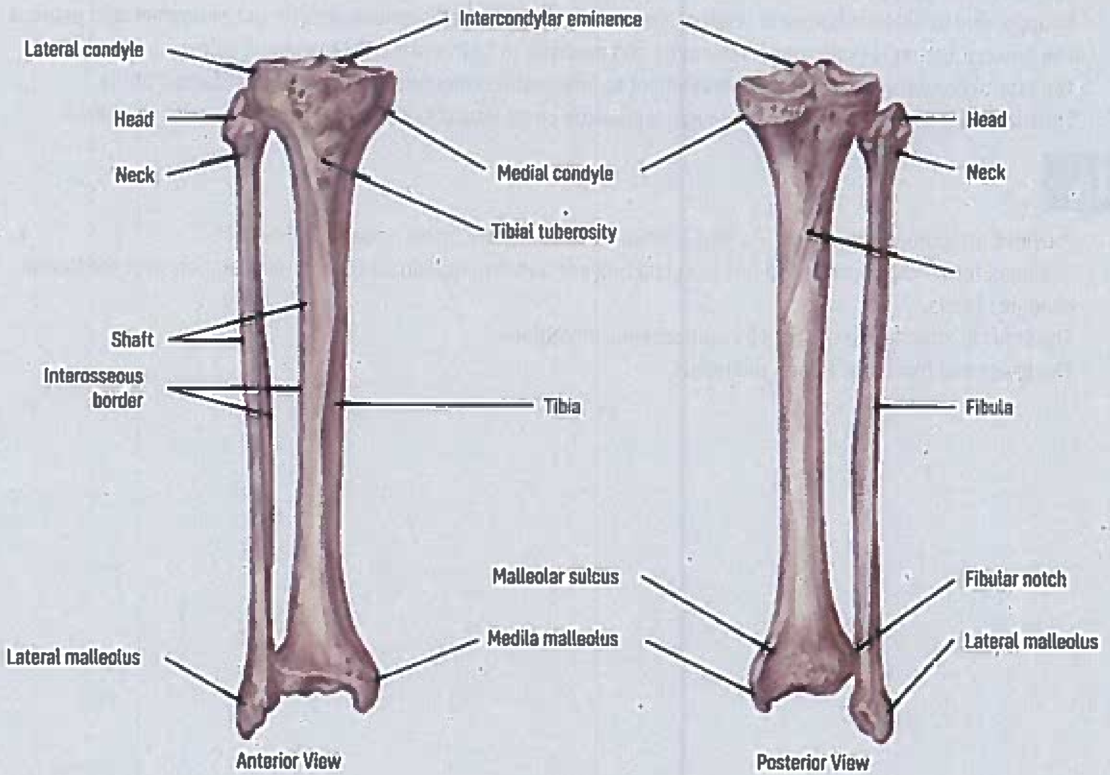
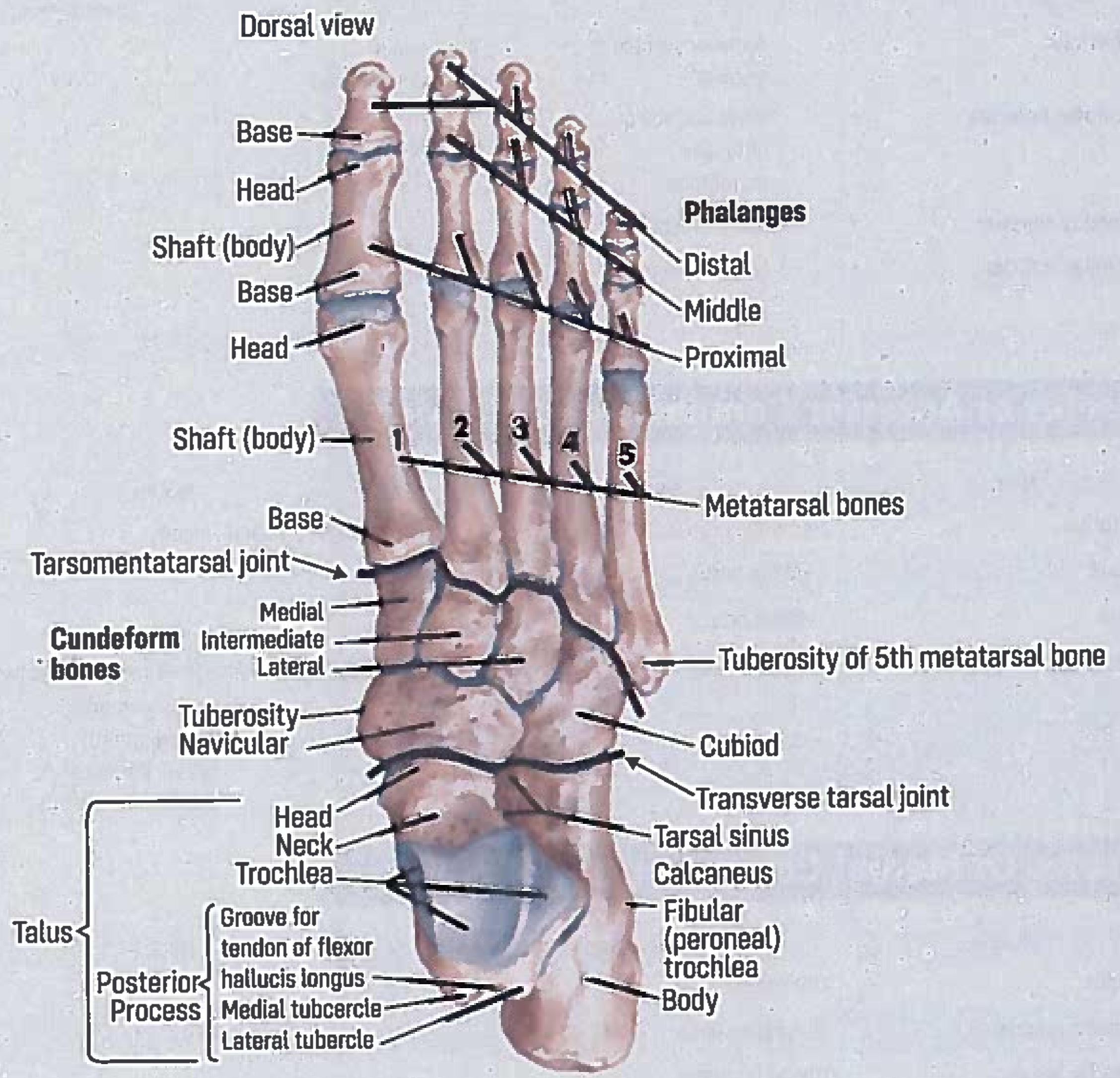


Tarsal Bones

- Lateral to medial, proximal to distal (**C**ute **T**ina **N**ever **C**ould **C**ooperate)
  - **Calcaneum: largest bone, forms prominence of heel**
  - **T**alus
  - **N**avicular
  - **C**uboid
  - **C**uneiform bones (3 in number)



Muscles of Lower Limb

Muscles of Gluteal Region

Muscle	Origin	Insertion	Nerve Supply
Gluteus Maximus	• Outer surface of ilium, sacrum, coccyx, sacrotuberous ligament	• Iliotibial tract and gluteal tuberosity of femur	• **Inferior gluteal nerve**
Gluteus medius	• Outer surface of ilium	• Lateral surface of greater trochanter of femur	• **Inferior gluteal nerve**

Gluteus minimus	• Outer surface of ilium	• Anterior surface of greater trochanter of femur	• Inferior gluteal nerve
Tensor fasciae latae	• Iliac crest	• Iliotibial tract	• Inferior gluteal nerve
Quadratus femoris	• Lateral border of ischial tuberosity	• Quadrate tubercle of femur	• All the following muscles has same nerve supply • Sacral plexus
Piriformis	• Anterior surface of sacrum	• All the four following muscles has common insertion i.e. • Upper border of greater trochanter of femur	
Obturator internus	• Inner surface of obturator membrane		
Gemellus superior	• Spine of ischium		
Gemellus inferior	• Ischial tuberosity		

Muscles of Anterior Compartment of Thigh

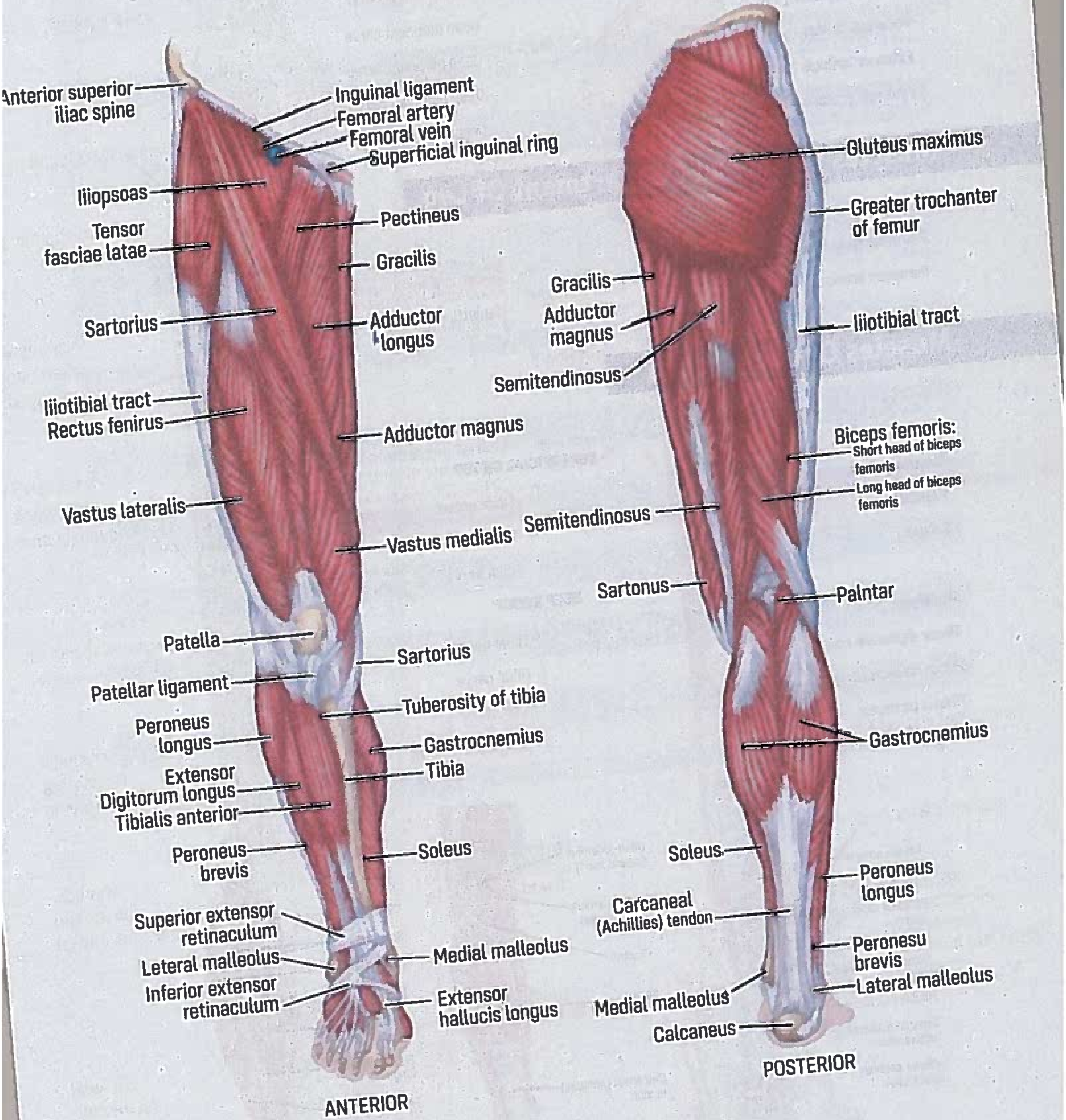
Muscle	Nerve Supply	Notes
Sartorius	Femoral nerve (L2, L3, L4)	Longest muscle in body
Iliacus	Femoral nerve	
Psoas	Lumbar plexus	
Quadriceps Femoris	Femoral nerve	Quadriceps Femoris → Includes 4 muscles • Rectus femoris • Vastus lateralis • Vastus medialis • Vastus intermedius

Muscles Of Medial Compartment Of Thigh

Muscle	Nerve Supply	Notes
Gracilis	Obturator nerve	
Adductor longus	Obturator nerve	
Adductor brevis	Obturator nerve	
Adductor magnus	Adductor portion → obturator nerve Hamstring portion → sciatic nerve	Because of its double nerve supply it is called as hybrid muscle
Obturator externus	Obturator nerve	

Muscle of Back of Thigh/ hamstring muscles

Muscle	Nerve Supply	Notes
Biceps femoris	**Long head:** tibial portion of sciatic nerve **Short head:** common peroneal portion of sciatic nerve	These 3 muscles on back of thigh are called hamstring muscles. All arises from ischial tuberosity.
Semitendinosus	Tibial portion of sciatic nerve	Insertion → bicep femoris on fibula while the other two on tibia.
Semimembranosus	Tibial portion of sciatic nerve	



Anterior superior iliac spine
Inguinal ligament
Femoral artery
Femoral vein
Superficial inguinal ring
Iliopsoas
Pectineus
Tensor fasciae latae
Gracilis
Sartorius
Adductor longus
Iiiotibial tract
Rectus fenirus
Adductor magnus
Vastus lateralis
Vastus medialis
Patella
Sartorius
Patellar ligament
Tuberosity of tibia
Peroneus longus
Gastrocnemius
Extensor Digitorum longus
Tibia
Tibialis anterior
Peroneus brevis
Soleus
Superior extensor retinaculum
Leteral malleolus
Medial malleolus
Inferior extensor retinaculum
Extensor hallucis longus
ANTERIOR
Gluteus maximus
Greater trochanter of femur
Gracilis
Adductor magnus
Iiiotibial tract
Semitendinosus
Biceps femoris:
Short head of biceps femoris
Long head of biceps femoris
Semitendinosus
Sartonus
Palntar
Gastrocnemius
Soleus
Peroneus longus
Carcaneal (Achillies) tendon
Peronesu brevis
Lateral malleolus
Medial malleolus
Calcaneus
POSTERIOR

Hip Joint

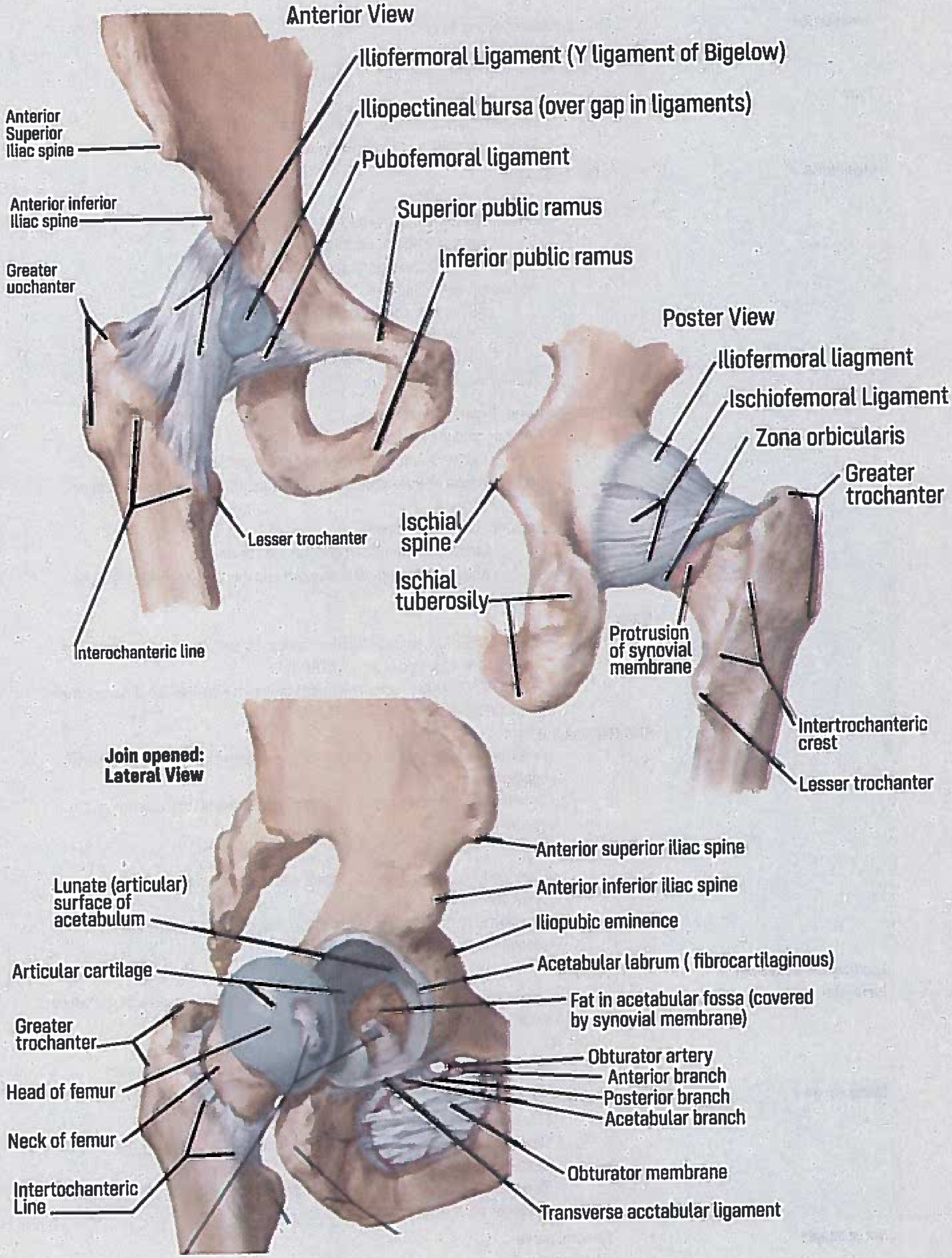
Articulation	• Head of femur + acetabulum of hip bone
Type	• Synovial ball and socket joint

Ligaments	• Illiofemoral ligament:
	  • Also called inverted y-shaped ligament of bigelow
	  • Prevents the trunk from falling backwards in standing posture
	  • Triangular , base attached to intertrochanteric line and apex to lower half of anterior iliac spine
	• Pubofemoral ligament
	• Ischiofemoral ligament
	• Ligament of head of femur (round ligament, or ligamentum teres)
	• Acetabular labrum
	• Transverse ligament of acetabulum

Blood supply	• Obturator artery • Medial and lateral circumflex femoral artery • Superior and inferior gluteal arteries
Nerve supply	• Femoral nerve • Anterior division of obturator nerve • Sciatic nerve • Nerve to quadratus femoris
Important relations	• Anteriorly→femoral nerve and vessels • Posteriorly→sciatic nerve

Movements of Hip Joint

Flexion	Extension	Abduction	Adductors	Lateral rotation	Medial rotation
Psoas major Illiacus Rectus femoris Sartorius Also adductor muscle	Gluteus maximus Hamstring muscles	Gluteus maximus Sartorius Tensor fascia lata Piriformis	Adductor longus Adductor brevis Adductor magnus Pectineus and gracilis	Piriformis Obturator externus and internus Superior and inferior gamelius Quadrator femoris Also gluteus maximus	Gluteus medius and minimus Tensor fascia lata.


Anterior View
Iliofermoral Ligament (Y ligament of Bigelow)
Iliopectineal bursa (over gap in ligaments)
Pubofemoral ligament
Superior public ramus
Inferior public ramus
Anterior Superior Iliac spine
Anterior inferior Iliac spine
Greater uochanter
Lesser trochanter
Interochanteric line
Poster View
Iliofermoral liagment
Ischiofemoral Ligament
Zona orbicularis
Greater trochanter
Ischial spine
Ischial tuberosily
Protrusion of synovial membrane
Intertrochanteric crest
Lesser trochanter
Join opened: Lateral View
Anterior superior iliac spine
Anterior inferior iliac spine
Iliopubic eminence
Acetabular labrum (fibrocartilaginous)
Fat in acetabular fossa (covered by synovial membrane)
Obturator artery
Anterior branch
Posterior branch
Acetabular branch
Obturator membrane
Transverse acctabular ligament
Lunate (articular) surface of acetabulum
Articular cartilage
Greater trochanter
Head of femur
Neck of femur
Intertochanteric Line

Knee Joint

Articulation

- Above→Condyles of femur
- Below→Condyles of tibia
- Front→Patella (femoral condyles articulate with patella in front)

Type

- Compound synovial joint
  - Between tibia and femur→synovial hinge joint
  - Between patella and femur→synovial gliding joint

Ligaments

- <u>**Extra-capsular**</u>
  - Ligamentum patellae
  - Lateral collateral ligament:
    - Above →lateral condyle of femur
    - Below→ head of fibula
  - Medial collateral ligament:
    - Above →medial condyle of femur
    - Below → medial surface of shaft of tibia.
    - It is strongly attached to medial meniscus
  - Oblique popliteal ligament:
- <u>**Inter-capsular (Cruciate ligaments)**</u>
  - Anterior cruciate ligament:
    - Below→Anterior intercondylar area of tibia
    - Above →Passes upward, backward, laterally to lateral femoral condyle
  - Posterior cruciate ligament:
    - Below Posterior intercondylar area of tibia
    - Above Passes upward, forward and medially to medial femoral condyle

<u>**Note:**</u>

- **ABL**→**ANTERIOR** cruciate ligament prevents **BACKWARDS** sliding of the femur on the tibia and inserts **LATERALLY**
- **PFM**→**POSTERIOR** cruciate ligament prevents **FORWARDS** sliding of the femur on the tibia and inserts **MEDIALLY**

<u>**Also remember it as:**</u>

- Anterior dislocation of tibia on femur is prevented by →anterior cruciate ligament
- Anterior dislocation of femur on tibia is prevented by →Posterior cruciate ligament.

- <u>**Menisci**</u>
  - C-shaped, Upper surfaces in contact with femoral condyles and lower with tibial condyles.
  - Function is to deepen the articular surfaces of tibial condyles to receive convex femoral condyles

Locking and unlocking of knee joint

- Locking
  - Locking is produced by continued action of the same muscles that produce extension i.e. quadriceps femoris
- Unlocking:
  - Unlocked by lateral rotation of femur brought by popliteus muscle

Blood supply

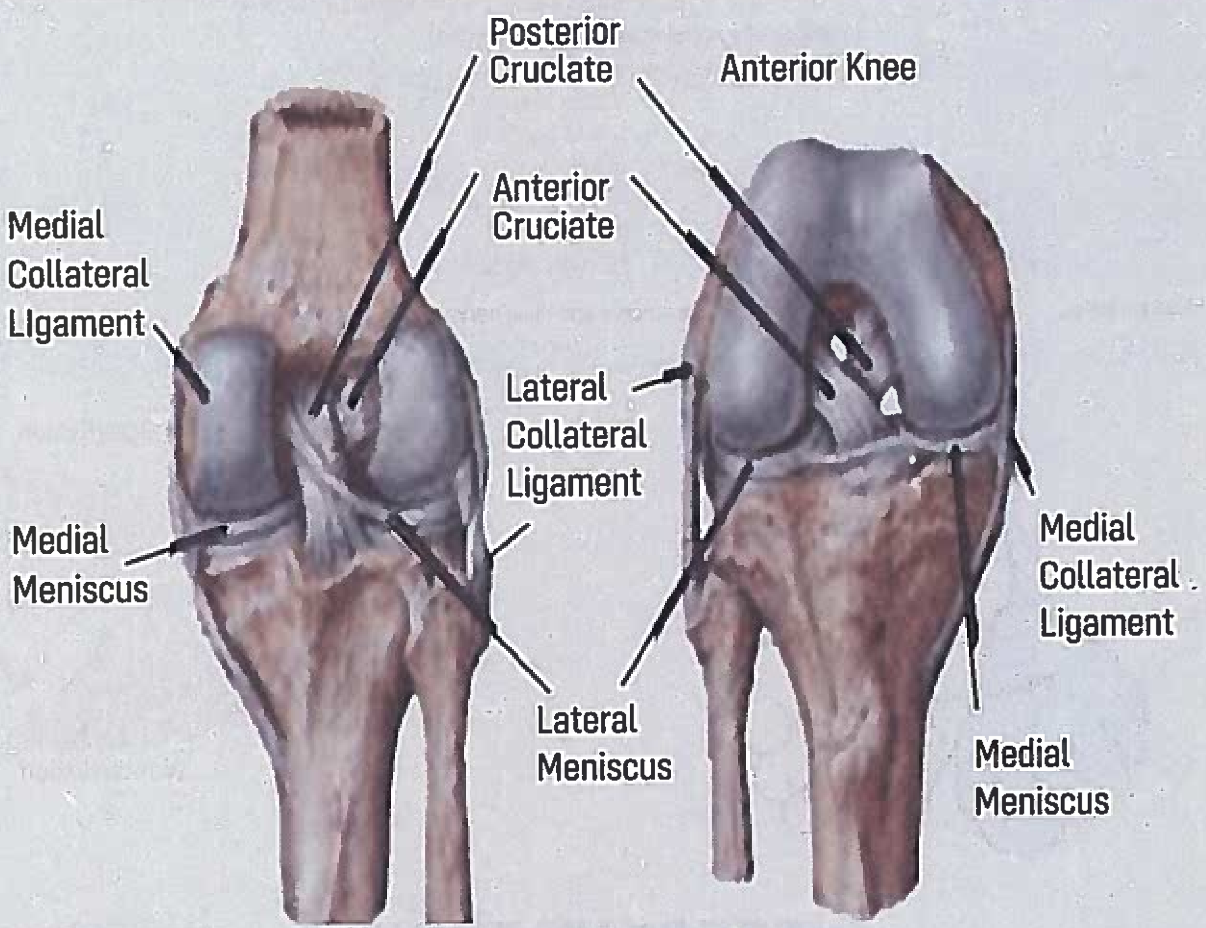
- Anastomosis around it
  - Five genicular branches of popliteal artery
  - Descending genicular branch of femoral artery
  - Descending branch of lateral circumflex femoral artery
  - Two recurrent branches of anterior tibial artery
  - Posterior tibial artery

Nerve supply

- Femoral nerve
- Sciatic nerve
- Obturator nerve

Movements of Knee Joint

Flexion	Extension	Medial rotation	Lateral rotation
• Biceps femoris • Semitendinous • Semimembranous • Also assisted by Gracilis, Sartorius and popliteal	• Quadriceps femoris	• Semitendinous • Semimembranous	• Biceps femoris



Ankle Joint

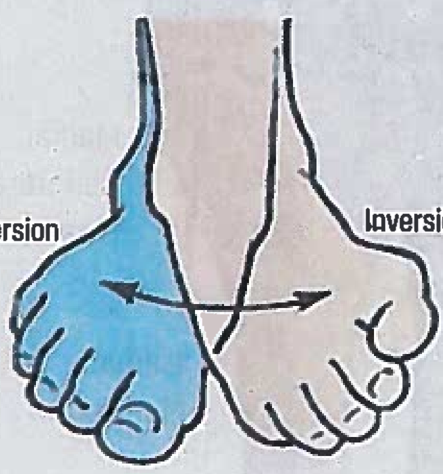
Articulation	• Above→
	  • Lower end of tibia including medial malleolus
	  • Lateral malleolus of fibula
	• Below →body of talus

Type	• Synovial hinge joint

Ligaments	• Medial (deltoid) ligament: b/w medial malleolus and talus
	• Lateral ligament; has three bands
	  • Anterior talofibular ligament
	  • Posterior talofibular ligament
	  • Calcaneofibular ligament

Movements	**Dorsiflexion of foot: (performed by muscles of anterior compartment)**
	• Tibialis anterior
	• Extensor halluces longus
	• Extensor digitorum longus
	• Peroneus
	Plantar flexion of foot: performed by posterior and lateral compartment.
	• Gastrocnemius
	• Soleus
	• Plantaris
	• Peroneus longus and peroneus brevis
	• Tibialis posterior
	• Flexor digitorum longus and flexor hallucis longus
	Inversion and eversion of leg (2nd letter rule)
	• Inversion of leg
	  • TIbialis anterior
	  • TIbialis posterior
	• Eversion of leg
	  • PEroneus Longus
	  • PEroneus Brevis
	  • PEroneus Tertius

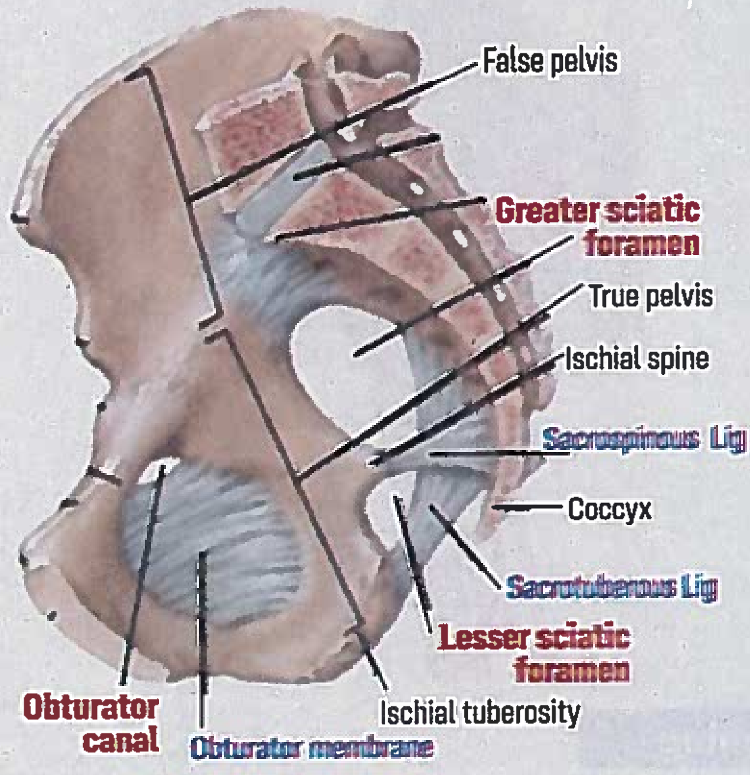
Nerve supply	• Deep peroneal nerve and tibial nerve.



DIFFERENT TOPICS

Greater Sciatic Foramen

- The greater sciatic foramen is formed by conversion of greater sciatic notch of hip bone into a foramen by the presence of sacrotuberous and Sacrospinous ligaments.
- Structures passing through the greater sciatic foramen:
  - The Piriformis
  - Above the Piriformis:
    - Superior gluteal nerve and vessels
  - Below the Piriformis: (**S**he **I**s **P**ossessive **I**n **N**ature)
    - **S**ciatic nerve
    - **I**nferior gluteal nerve and vessels
    - **P**osterior cutaneous nerve of thigh.
    - **P**udendal nerve
    - **I**nternal pudendal vessels
    - **N**erve to quadratus femoris and obturator internus.



Lesser Sciatic Foramen

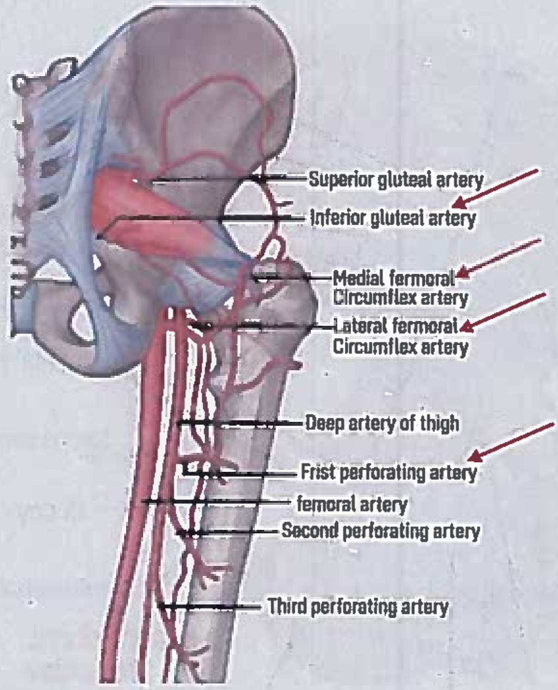
- Formed by sacrotuberous and Sacrospinous ligament
- Structures passing through it:
  - Tendon of obturator internus
  - Nerve to obturator internus
  - Pudendal nerve
  - Internal pudendal vessels.

Trochanteric Anastomosis

- Location →near trochanteric fossa
- Supplyhead→ of femur
- Connection b/w →Internal iliac and femoral artery
- Formed by
  - Superior gluteal artery
  - Inferior gluteal artery
  - Medial and lateral circumflex femoral artery (ascending branch)

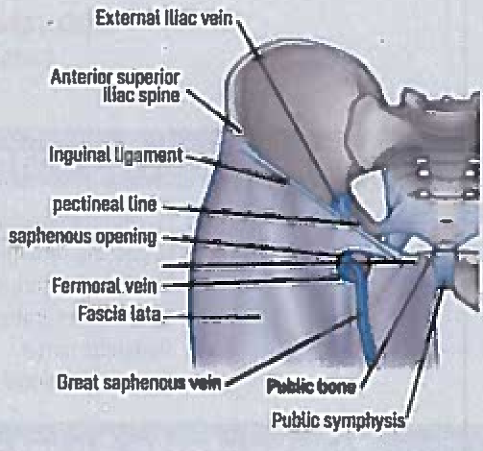
Cruciate Anastomosis

- Location →at level of lesser trochanter on back of femur
- Connection between→ internal iliac and femoral artery
- Formed by
  - Inferior gluteal artery
  - Medial and lateral circumflex femoral artery (transverse branch)
  - First perforating branch of profunda femoris artery



Saphenous Opening

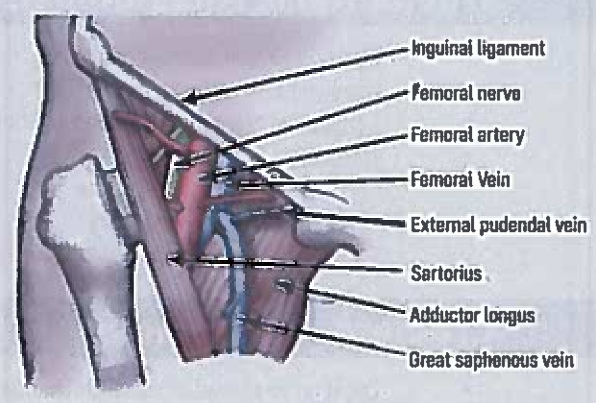
- Opening in deep fascia in front if thigh just below inguinal ligament.
- Contents:
  - Great saphenous vein
  - Small branches of femoral artery
  - Lymph vessels.
- Saphenous opening is filled with loose connective tissue called cribriform fascia



Femoral Triangle

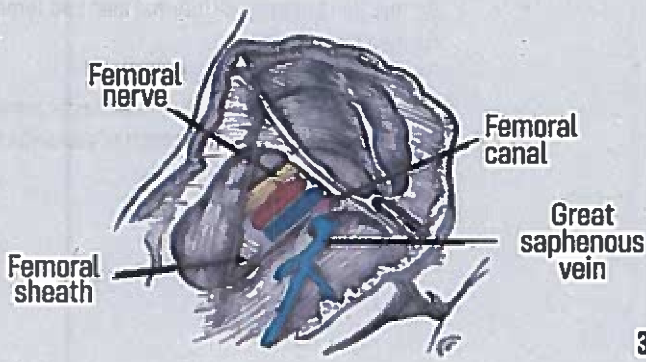
- Boundaries:
  - Laterally: medial border of Sartorius
  - Medially: medial border of adductor longus
  - Base: inguinal ligament
  - Apex: joining of medial and lateral border
- Contents:

Mnemonics: **You go from lateral to medial to find your NAVEL.**
(**NAVEL**- from lateral to medial)



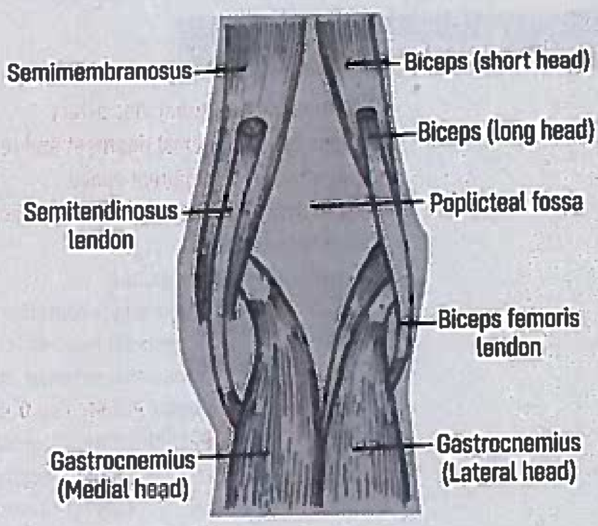
Femoral Sheath

- Downward protrusion from abdomen into thigh of fascia transversalis (anterior wall) and fascia iliaca (posterior wall).
- It covers the femoral vessels but not nerve
- Compartments:
  - Lateral compartment: Femoral artery
  - Intermediate compartment: Femoral vein
  - Medial compartment: Femoral canal (Base or upper end of femoral canal is called femoral ring)



Popliteal Fossa

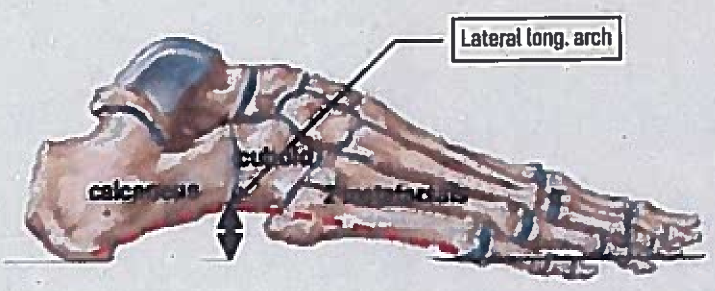
- Diamond shaped intermuscular space lying behind knee joint
- Boundaries:
  - Superolaterally: biceps femoris
  - Superomedially: Semimembranous and Semitendinous
  - Inferolaterally: gastrocnemius (lateral head), Plantaris
  - Inferomedially: gastrocnemius (medial head)
- Contents:
  - Popliteal artery and its branches
  - Popliteal vein and its tributaries
  - Tibial and common peroneal nerve
  - Posterior cutaneous nerve of thigh
  - Small saphenous vein
  - Connective tissue
  - Lymph nodes.

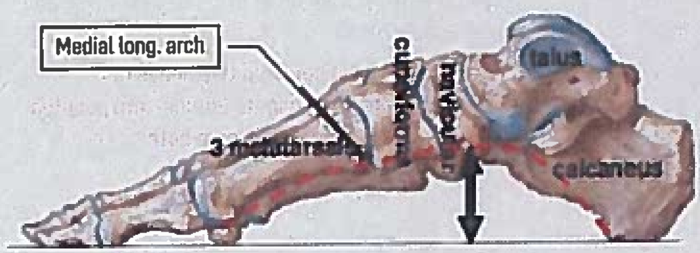


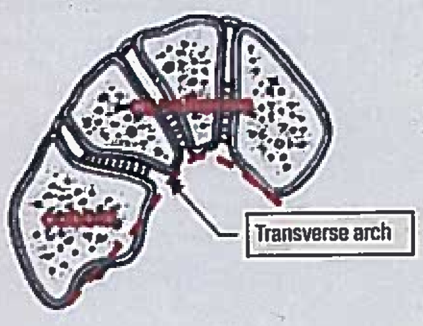
Boundaries of Popliteal Fossa

Arches of Foot

Medial Longitudinal Arch	Formed by Calcaneum, talus, Navicular bone, 3 cuneiform bones, and first 3 metatarsal bones. Anterior Pillar: Medial 3 metatarsal bones Posterior Pillar: Calcaneum Key stone: Talus
Lateral Longitudinal Arch	Formed by Calcaneum, cuboid, and 4th 5th metatarsal bones Anterior Pillar: 4th and 5th metatarsal bones Posterior Pillar: Calcaneum Key stone: Talus
Transverse Arch	Formed by bases of metatarsal bones, cuboid, 3 cuneiform bones







Arteries of Lower Limb

Femoral Artery

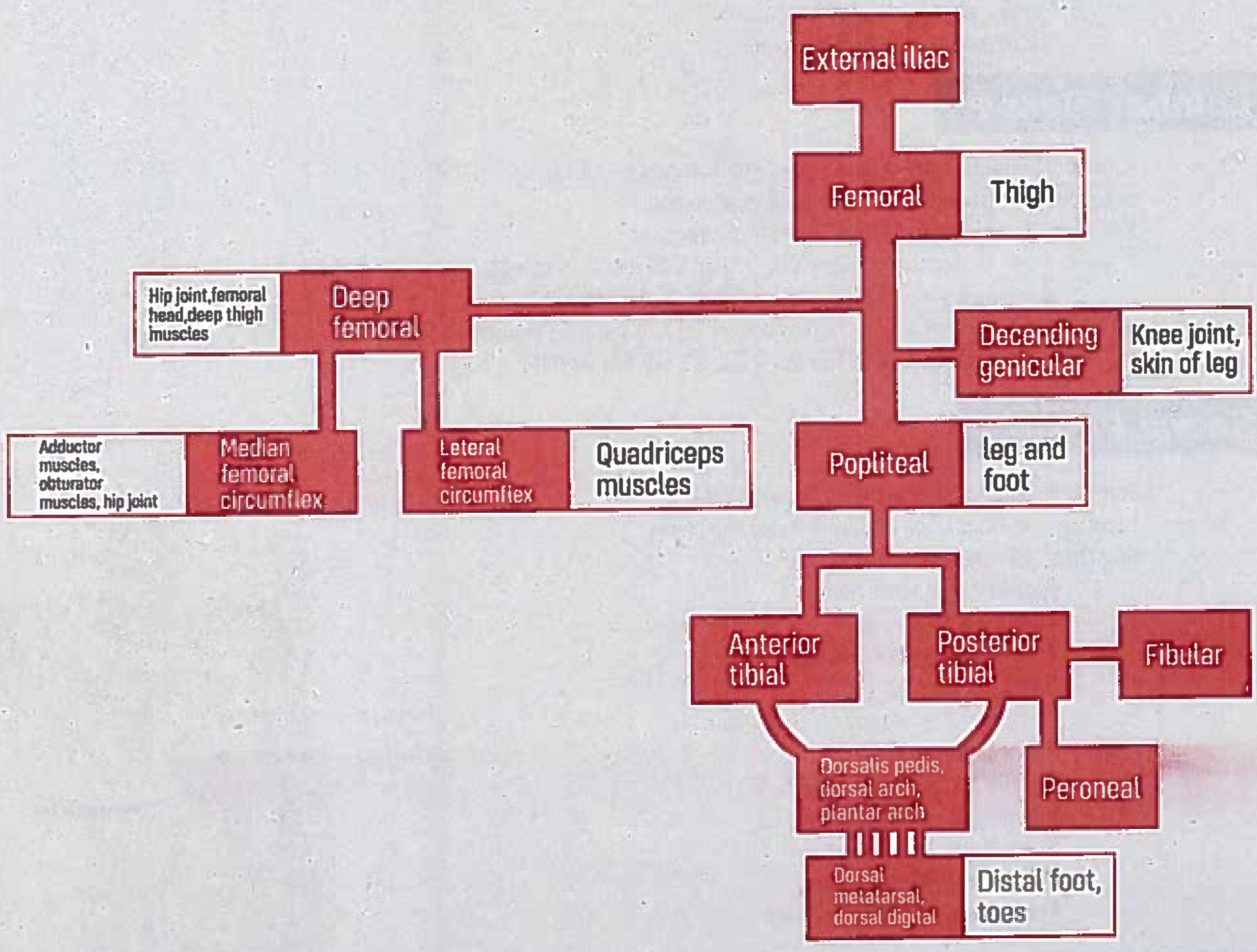
- Continuation of external iliac artery
- It begins behind inguinal ligament and terminates at adductor hiatus (opening in adductor magnus), and continue as popliteal artery in popliteal space.
- It lies midway between anterior superior iliac spine and symphysis pubis.
- Branches:
  - Superficial branches:
    - Superficial circumflex iliac artery
    - Superficial epigastric artery
    - Superficial external pudendal artery.
  - Deep branches: "**P**ut **M**y **L**eg **D**own **M**adam'
    - Profunda femoris artery (further divides into)
      - **M**edial circumflex femoral artery
      - **L**ateral circumflex femoral artery
    - **D**escending genicular artery
    - **M**uscular arteries.

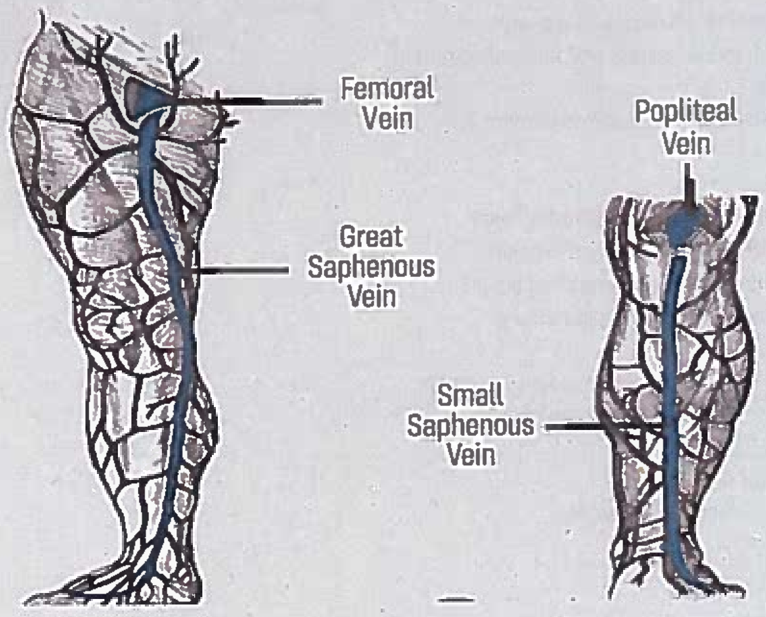
Popliteal Artery

- Continuation of femoral artery
- It begins at adductor hiatus and terminate at lower border of popliteus muscle by dividing into anterior and posterior tibial arteries.
- <u>Anterior Tibial Artery</u>
  - It descend with deep peroneal nerve to front of ankle joint from anterior compartment, where it becomes dorsalis pedis artery.
  - Dorsalis pedis artery:
    - Begins in front of ankle, joins lateral plantar artery and complete the plantar arch.
  - <u>Posterior Tibial Artery:</u>
    - Descends in posterior compartment and is accompanied by tibial nerve.
    - Peroneal arterylarge artery, arises from and close to origin of posterior tibial artery.
    - Terminates behind medial malleolus into medial and lateral plantar arteries.

Veins of Lower Limb

Great Saphenous Vein	Small Saphenous Vein
• Arises from Medial side of dorsal venous arch.	• Arises from Lateral part of dorsal venous arch.
• Ascend upward in front of medial malleolus	• Ascends behind the lateral malleolus
• Accompanied by saphenous nerve in superficial fascia	• Accompanying sural nerve
• Runs upward along medial side of leg, passes behind knee and curves forward around medial side of thigh	• Ascends with lateral border of tendo calcaneus and in the middle of leg
• Drains into femoral vein (in saphenous opening)	• Pierces deep fascia between two heads of gastrocnemius and terminate (drains) into popliteal vein or great saphenous vein or in both


External iliac
Femoral
Thigh
Hip joint,femoral head,deep thigh muscles
Deep femoral
Decending genicular
Knee joint, skin of leg
Adductor muscles, obturator muscles, hip joint
Median femoral circumflex
Leteral femoral circumflex
Quadriceps muscles
Popliteal
leg and foot
Anterior tibial
Posterior tibial
Fibular
Dorsalis pedis, dorsal arch, plantar arch
Peroneal
Dorsal metatarsal, dorsal digital
Distal foot, toes


Femoral Vein
Great Saphenous Vein
Popliteal Vein
Small Saphenous Vein

Nerves of Lower Limb

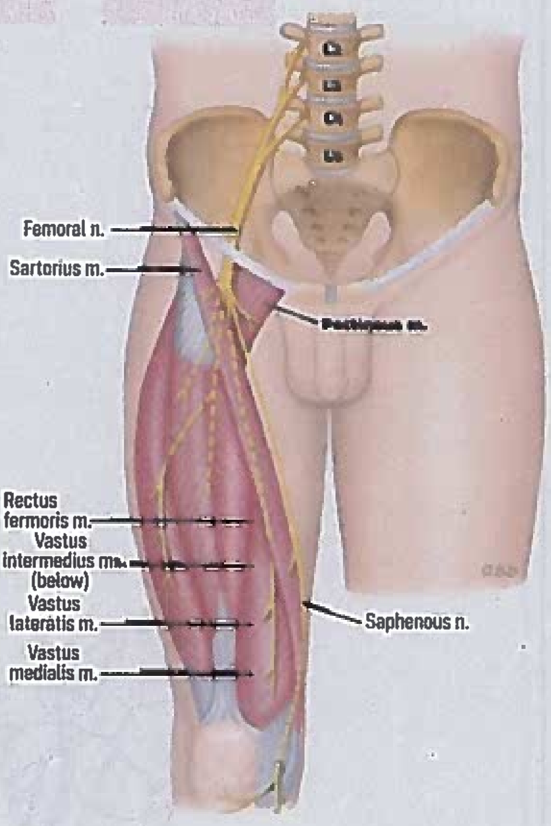
- Nerves of the lower limb originate from
  - Lumbar plexus (situated in abdomen)
  - Sacral plexus (situated in pelvis).

Lumbar Plexus

- Formation: Anterior rami of upper four lumbar nerves L1, L2, L3, L4.
- Location: in substance of psoas muscle, in abdomen
- Branches: (**I**nterested **I**n **G**etting **L**unch **O**n **F**ridays)
    - Lumbar plexus roots "2 from 1, 2 from 2, 2 from 3":
  - 2 nerves from 1 root: **I**lioinguinal (L1), **I**liohypogastric (L1).
  - 2 nerves from 2 roots: **G**enitofemoral (L1, L2), **L**ateral Femoral (L2, L3).
  - 2 nerves from 3 roots: **O**bturator (L2, L3, L4), **F**emoral (L2, L3, L4).

Sacral Plexus

- Formation: anterior rami of L4, L5, S1, S2, S3,S4
- Location: it is situated on Piriformis muscle in pelvis.
- Branches: (**6 P**reacher's **SINS**)
  - **P**osterior cutaneous nerve
  - **P**elvic splanchnic nerve
  - **P**udendal nerve **(S2, S3, S4)**
  - Nerve to **P**iriformis (S1, S2)
  - **P**erforatory cutaneous nerve of thigh
  - **P**erineal branch of S4
  - **S**uperior gluteal nerve (L4, L5, S1)
  - **I**nferior gluteal nerve (L5, S1, S2)
  - **N**erve to obturator internus
  - **N**erve to quadratus Femoris
  - **S**ciatic nerve (L4, L5, S1,S2, S3)



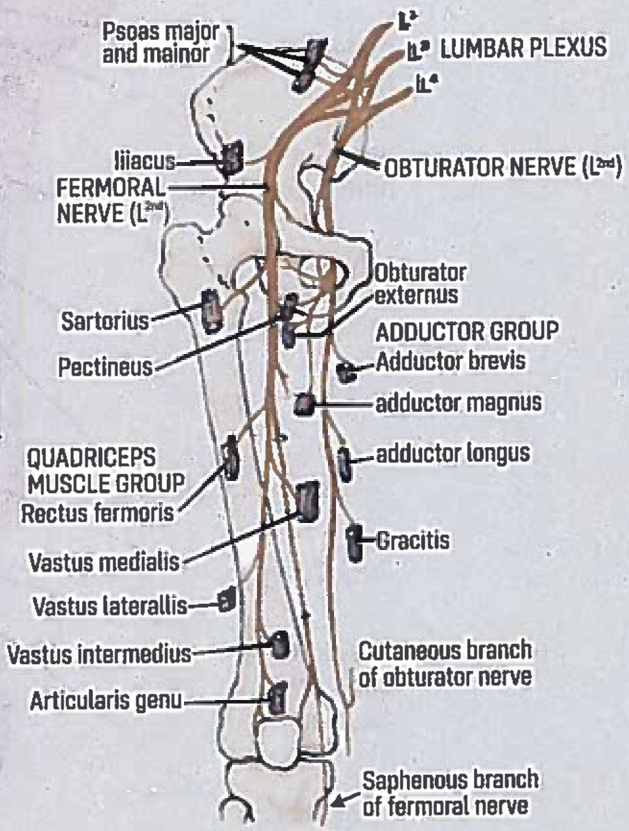
Femoral Nerve

- **Arises from L2, L3, L4**
- It enters thigh behind the inguinal ligament
- It lies lateral to femoral vessels and femoral sheath in femoral triangle
- It quickly terminates by dividing into anterior and posterior divisions.
- Branches:
  - Muscular branches: **To Anterior Facial Compartment** (except psoas major).
  - Articular branches: to knee and hip joint
  - Vascular branches: Femoral artery
  - Anterior divisions:
    - Medial cutaneous nerve of thigh
    - Intermediate cutaneous nerve of thigh.
  - Posterior divisions:
    - Saphenous nerve.

Obturator Nerve

- Arises from lumbar plexus L2, L3, L4
- And runs forward on the lateral wall of the pelvis to reach the obturator canal (the upper part of obturator foramen).
- Branches →The obturator nerve divides into anterior and posterior divisions

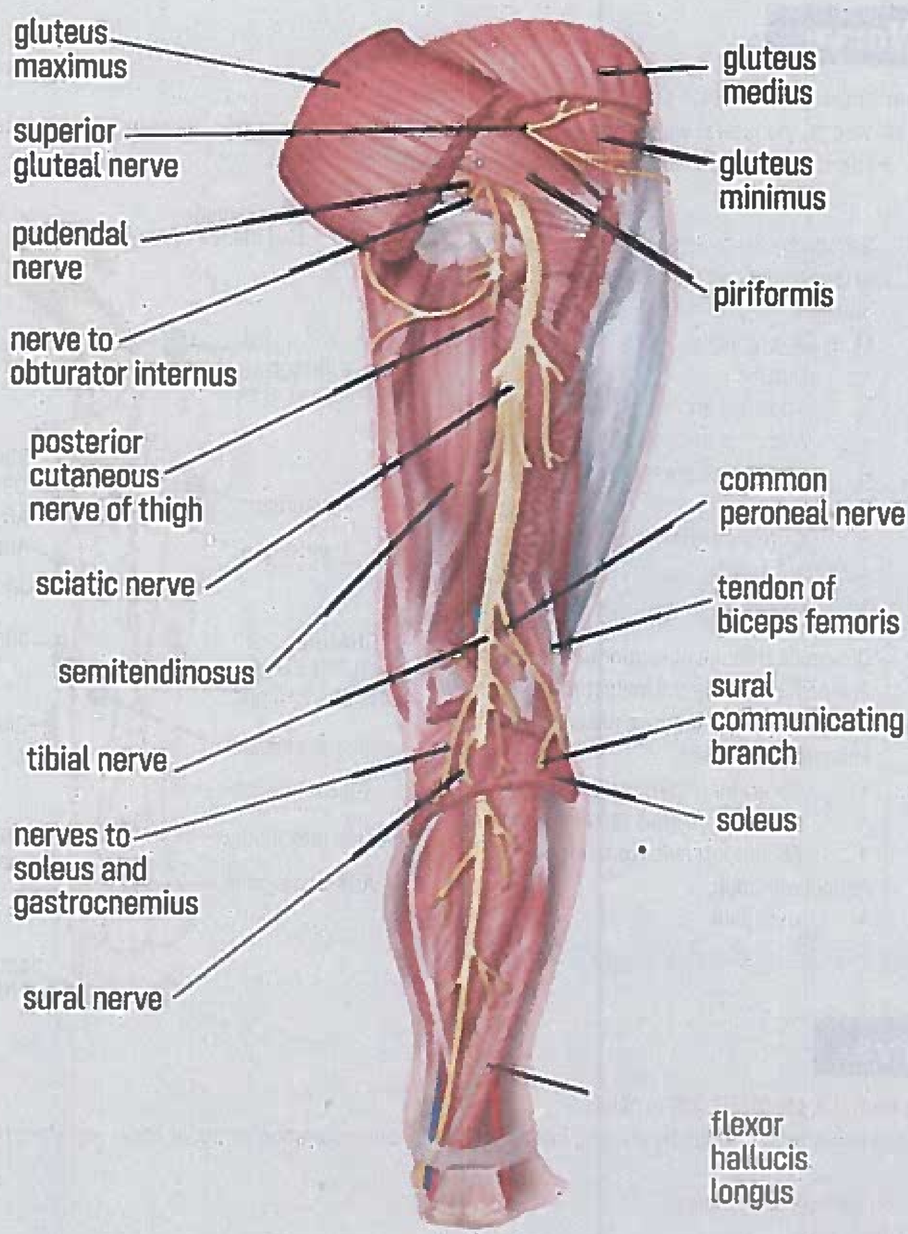
Anterior divisions	Descends into thigh anterior to the obturator externus and adductor brevis muscles. Muscular branches: • Gracilis • Adductor brevis • Adductor longus • Sometimes pectineus muscle Cutaneous: • Skin on medial side of thigh Articular branch: • Hip joint
Posterior division	Descends through obturator externus muscle and passes behind the adductor brevis and in front of adductor magnus muscles Muscular branches: • Obturator externus • Adductor magnus (adductor part) • Adductor brevis (sometimes) Articular branch: • knee joint



Sciatic Nerve

- Originate from (L4, L5, S1, S2, S3) in pelvis
- Terminate in lower third of thigh by dividing into terminal branches; common peroneal nerve and tibial nerve.
- Branches:
  - Common peroneal nerve
  - Tibial nerve
  - Muscular branches to hamstring muscles
- Common peroneal nerve:
  - Originate in lower third of thigh
  - Winds laterally around neck of fibula
  - Terminates by piercing peroneus longus and divides into terminal branches
  - Branches

Muscular branch	Short head of biceps femoris
Articular branch	knee joint
Cutaneous branch	Sural communicating and Lateral cutaneous nerve of calf
Terminal branch	Superficial peroneal nerve and Deep peroneal nerve



Clinical Anatomy

Nerve Injury

Nerve injury	Presentation
Common peroneal nerve	• Fracture of neck of fibula results in injury to common peroneal nerve • **PED** = Peroneal Everts and Dorsiflexes • If injured, results in foot Dropped
Tibial nerve	• **TIP** = Tibial Inverts and Plantarflexes • If injured, can't →Stand on **TIP** of Toes

Superior gluteal nerve	• Common cause: intra-gluteal injections
	• Results in paralysis of →gluteus medius and minimus
	• Trendelenburg's test:
	  ▪ Normally when the body weight is supported on one limb, the glutei of the supported side raise the opposite unsupported side of pelvis.
	  ▪ However, if abductor mechanism is defective, the unsupported side of pelvis drops, this is known as a positive Trendelenburg's test.
	  ▪ It is caused by paralysis of gluteus medius, dislocation of hip joint, or fracture of neck of femur.

	• Patient cannot walk normally. • Sways (waddles) on paralyzed side to clear the opposite foot of the ground. This is known as lurching gate; when bilateral it is called waddling gate. • Unilateral positive Trendelenburg's sign produces a lurching gait • Bilaterally positive Trendelenburg's sign produces a waddling gait.
Inferior gluteal nerve	• Paralysis of → Gluteus Maximus • Patient cannot stand from sitting position without support, Difficulty climbing stairs, loss of Hip extension

Blood Supply of Femur

- Blood supply of head of femur
  - Adults (Retinacular artery > medial circumflex artery)
  - Children (obturator artery)
- Blood supply of neck of femur → Medial and lateral circumflex artery

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Chapter 3: Thorax

Bones

Sternum

- Flat bone divided into 3 parts

Manubrium	• Articulation
	  • body of sternum (manubriosternal joint)
	  • Clavicle, 1st and 2nd costal cartilage on each side
	• Sternal angle (angle of Louis- T4 level):
	  • Formed by articulation of manubrium with body of sternum.
	  • It lies at level of
	    • Second costal cartilage
	    • Bifurcation of trachea
	    • Junction of ascending aorta and aortic arch and junction of aortic arch and descending thoracic aorta.
	    • Junction of superior mediastinum and inferior mediastinum

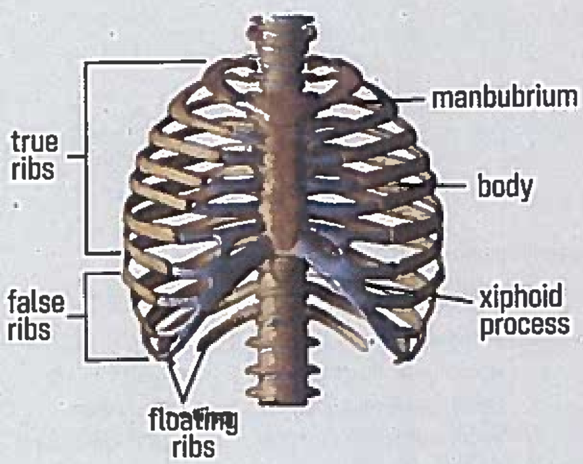
Sternum	• Above: manubrium (manubriosternal joint) • Below: xiphoid process (xiphisternal joint)
Xiphoid process	• Thin plate of cartilage, no ribs or costal cartilage are attached to xiphoid process

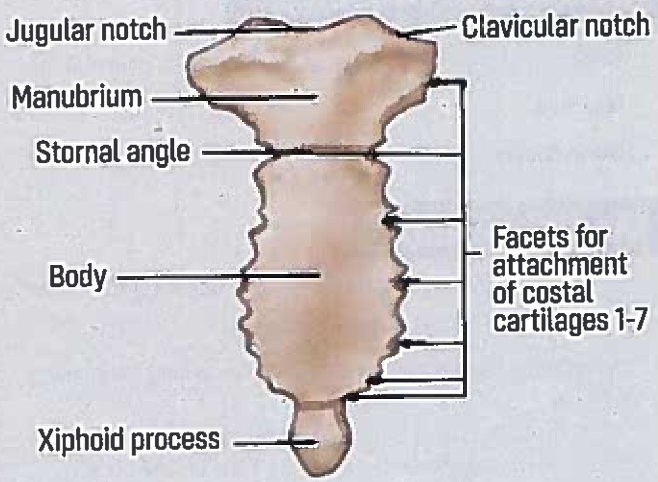
Ribs

- 12 pairs of ribs
- True ribs →upper seven pairs are attached to sternum by their costal cartilages
- False ribs →8th, 9th, 10th pair's area attached anteriorly to each other and to 7th rib by their costal cartilages.
- Floating ribs→ 11th and 12th pair have no anterior attachments

Costal Cartilages

- Connect the upper 7 ribs to sternum and 8-10 ribs to cartilage immediately.





Muscle of Thoracic Wall

Diaphragm

Shape	• Anteriorly: dome shaped • Above: kidney shaped • Sagittal view: j-shaped

Origins of diaphragm	3 parts
	• **Sternal part:**
	  ◦ Right and left slips arise from posterior surface of xiphoid process
	• **Costal part:**
	  Six slips arise from lower six ribs and their costal cartilages
	• **Inversion and eversion of leg (2nd letter rule)**
	  • From Crura and arcuate ligament
	    ◦ Right Crura: from L1, L2, L3 and their intervertebral discs
	    ◦ Left Crura: from L1, L2 and their intervertebral discs.
	    ◦ Two Crura are connected by median arcuate ligament.
	  • Arcuate ligament:
	    ◦ Medial arcuate ligament: thickened fascia covering ant surface of psoas muscle
	    ◦ Lateral arcuate ligament: thickened fascia covering ant surface of quadratus lumborum muscle

Insertion	• Inserted into a central tendon which is trefoil in shape at level of xiphisternal joint • Fused with inferior surface of fibrous pericardium
Nerve supply	• Phrenic nerve (C3, 4, 5)
Arterial supply	• Lower five intercostal arteries • Subcostal artery (T12) • Right and left inferior phrenic artery (from abdominal aorta) • Pericardiophrenic artery • Musculophrenic artery

Opening in diaphragm (V.O.A)	Just count the number of letters and you'll remember opening
	• Vena-cava opening (T8 level)
	  ◦ Structures passing → Inferior vena cava and phrenic nerve
	• Oesophagus opening (T10 level)
	  ◦ Structures passingOesophagus, Vagus nerve (CN-10), Left gastric artery,
	• Aortic hiatus (T12 level)—red, white, blue
	  ◦ Structures→ Aorta(red), Thoracic duct (white), Azygous vein(blue)

Intercostal Muscles

Origin	• Inferior border of Rib
Insertion	• Superior border of Rib
Nerve Supply	• Intercostal Nerve

Mediastinum

- The mediastinum is the median septum of the thorax between the two lungs.

Superior Mediastinum	**Inferior Mediastinum**
Is separated from inferior mediastinum by an imaginary line passing • Anteriorly →through sternal angle • Posteriorly →through lower body of 4th thoracic	Subdivided into three parts by pericardium • Anterior mediastinum →in front of pericardium • Posterior mediastinum →behind pericardium • Middle mediastinum→ formed by pericardium and its contents

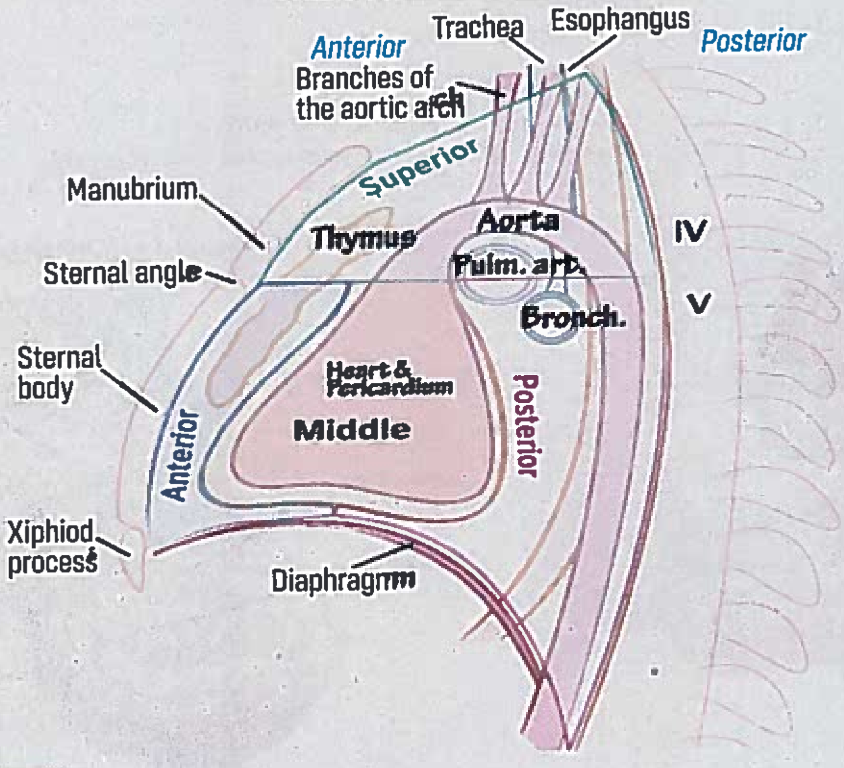
Contents Of Superior Mediastinum

(PVT (PriVaTe) Left BATTLE

- **P**hrenic nerve
- **V**agus nerve
- **T**horacic ducts
- **Left** recurrent laryngeal nerve.(Not the right)
- **B**rachiocephalic vein
- **A**ortic Arch (and its branches)
- **T**hymus
- **T**rachea
- **L**ymph node
- **E**sophagus

- **Contents of Anterior Mediastinum:**
  - Sternopericardial ligaments
  - Lymph nodes
  - Thymus
- **Contents of Middle Mediastinum:**
  - Heart
  - Bifurcation of trachea
  - Ascending aorta
  - Pulmonary trunk (arteries and veins)
  - Terminal part of azygous vein
  - Phrenic nerve
- **Contents of Posterior Mediastinum (DATES)**
  - **D**escending aorta
  - **A**zygous vein and Hemiazygous vein.
  - **T**horacic duct
  - **E**sophagus.
  - **S**ympathetic trunk/ganglia.

The Mediastinum



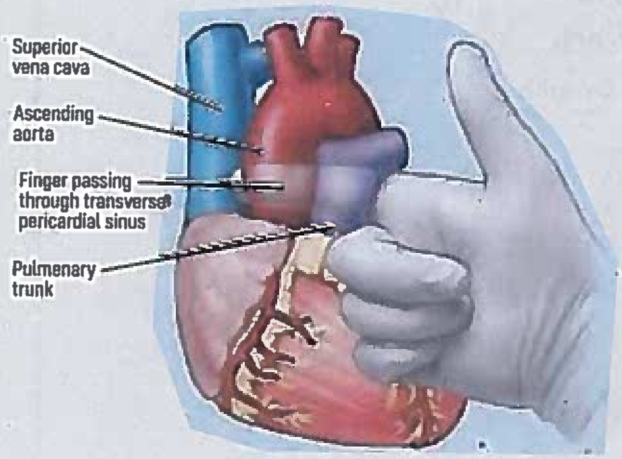
Pericardium

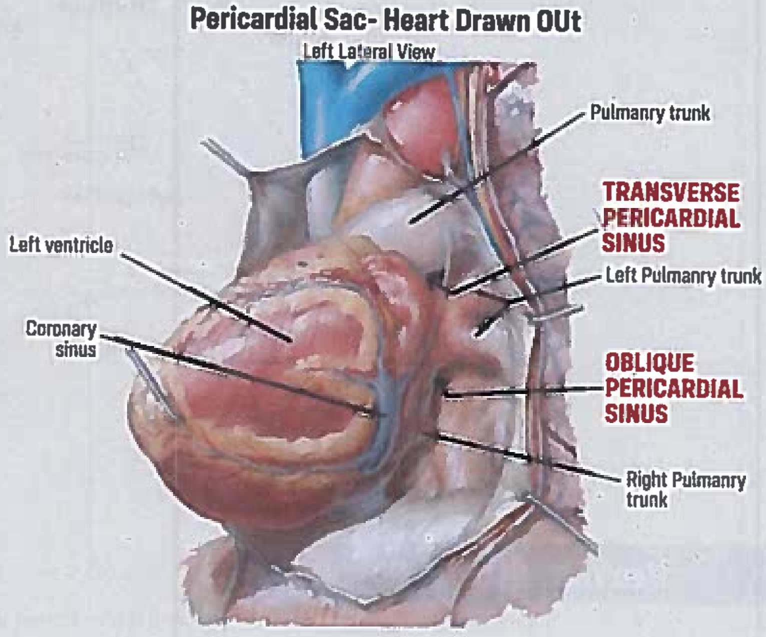
- Fibrous sac, which encloses the heart and roots of great vessels.
- It lies within middle mediastinum

Consists of

- Fibrous pericardium:
  - It is strong and limits unnecessary movements of heart.
  - Apex→ lies at level of sternal angle. It fuses above with the walls of great vessels (ascending aorta, pulmonary trunk, SVC, IVC, and pulmonary veins).
  - Base →central tendon of diaphragm.
  - Anteriorly→ sternum by Sternopericardial ligament
  - Posteriorly →related to principal bronchi, the esophagus and descending aorta.
  - On each side mediastina pleura, mediastinal surface of lung.

Consists of	• <u>Serous pericardium:</u> • It is thin double layered serous membrane lined by mesothelium. • The outer layer parietal pericardium is fused with fibrous pericardium • The inner layer visceral pericardium or epicardium is fused to heart.
Pericardial cavity	• Space b/w parietal pericardium and visceral pericardium. • Contains serous fluid which lubricates and facilitate cardiac movements
Sinuses of pericardium	• Transverse sinus: • Horizontal gap between arterial and venous ends of heart tube. • Bounded • anteriorly by → ascending aorta and pulmonary trunk • posteriorly by → superior vena cava and left atrium • Oblique sinus: • Narrow gap behind heart • Bounded • Anteriorly → left atrium • Posteriorly → parietal pericardium
Arterial supply	The fibrous and parietal pericardia are supplied by • Internal thoracic • Musculophrenic arteries • Descending thoracic aorta
Nerve supply	• Fibrous and parietal pericardium: phrenic nerve • Visceral pericardium: autonomic nerves (not sensitive to pain).





Heart

• Conical hollow muscular organ situated in middle mediastinum

External features	• **Four chambers** → right and left atria, and right and left ventricles • **3 surfaces** → Anterior (sternocostal), Inferior (diaphragmatic), Posterior (base of heart formed by left atrium and small part by right atrium) • **Apex:** • Formed by left ventricle situated at 5th intercostal surface 3.5 inches (8 cm) lateral to midline(sternum) and just medial to midclavicular line

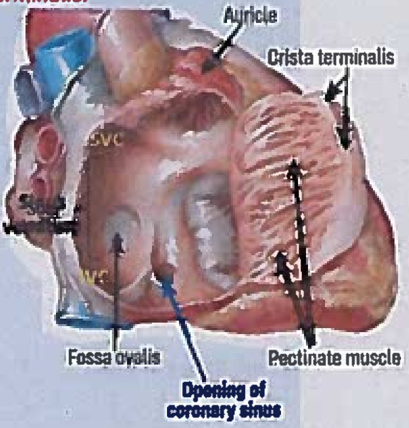
<table>
<tr><td>Right Atrium</td><td>

Consists of 2 parts, main cavity and an auricle
Externally, at the junction of two parts a shallow groove called sulcus terminalis present.
Sulcus terminalis on inside forms a ridge called cristae terminalis.
<u>Openings:</u>

Superior vena cava (no valve)
Inferior vena cava (rudimentary valve exists)
Coronary sinus (rudimentary valve exists)
Right atrioventricular orifice (tricuspid valve).
Anterior cardiac veins

<u>Fetal remnants:</u>

In addition to rudimentary valve of IVC there are also
Fossa ovalis:
A shallow depression on septal wall, which is the site of foramen ovale in fetus
Annulus ovalis
Prominent upper margin of fossa ovalis



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<tr><td>Right ventricle</td><td>

Inflowing part →guarded by atrioventricular orifice
Outflowing part/infundibulum→ opens into pulmonary trunk, pulmonary valve present
Trabeculae carnea

Three types:

Ridges
Bridges: →moderator band: muscular bridges that crosses the ventricular cavity from septal to anterior wall.it conducts right branch of A.V bundle
Papillary muscles (shown in fig below)

Their base attached to ventricular wall.
Apex connected by fibrous cord (chordae tendineae) to cusps of tricuspid valve

</td></tr>
<tr><td>Left atrium</td><td>

Consists of main cavity and auricle
Openings:

Four pulmonary veins (devoid of valves)
Left Atrioventricular orifice (mitral valve--bicuspid)

</td></tr>
<tr><td>Left ventricle</td><td>

Walls 3 times thicker than right ventricle
Openings:
Left AV orifice (bicuspid-mitral valve) and Aortic orifice (aortic valve)

</td></tr>
<tr><td>Valves of heart</td><td>

Atrioventricular valves: tricuspid and bicuspid
Semilunar valves: aortic and pulmonary valves

</td></tr>
<tr><td>Arterial supply</td><td>

<u>Right coronary artery:</u>

Arises from the anterior aortic sinus
Runs between pulmonary trunk and right auricle
Runs in the atrioventricular groove
Continues in posterior atrioventricular groove to anastomose with left coronary artery.
Branches:

Marginal
Posterior interventricular
Right atrial

Supplies:

Right atrium and right ventricle
Whole conducting system of heart

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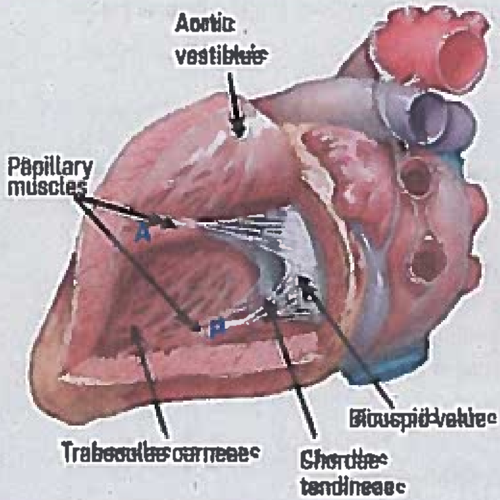
</table>

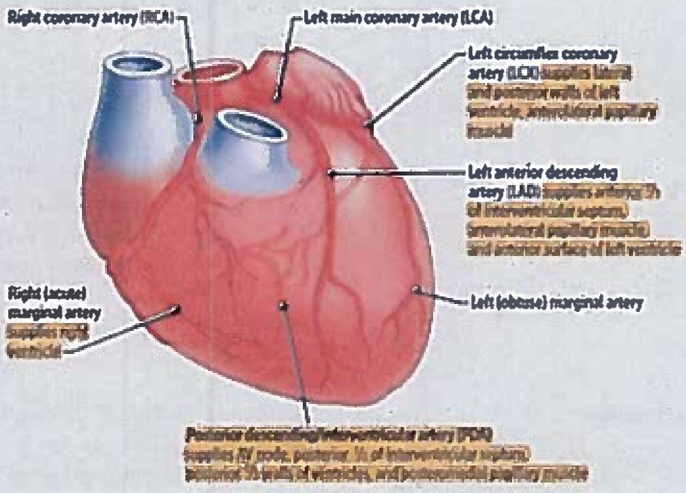
	• Left coronary artery:
	  • Arises from left posterior aortic sinus
	  • Branches:
	    • Anterior interventricular artery
	    • Circumflex artery
	  • Supplies:
	    • Left atrium and left ventricles
	    • A part of left branch of AV bundle.

Venous drainage	• Coronary sinus
	  • Ends by opening into right atrium
	  • Tributaries:
	    • Great cardiac vein, middle cardiac vein. Small cardiac veins and smaller veins

Lymphatics of heart	• Right trunk of lymphatic ends into brachiocephalic nodes • Left trunk of lymph nodes ends into tracheobronchial lymph nodes
Nerve supply	• Superficial and deep cardiac plexuses

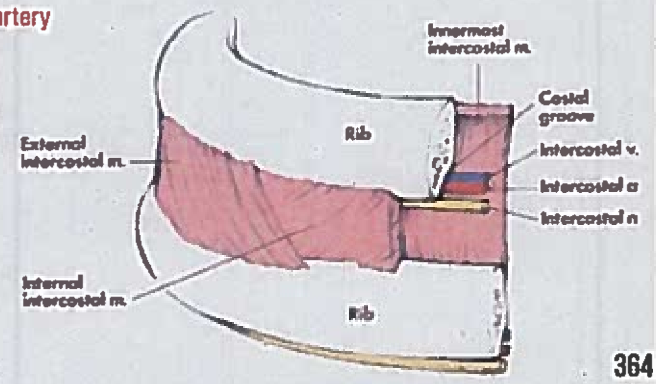
Note → The most posterior part of the heart is the left atrium; enlargement can cause dysphagia (due to compression of the esophagus) or hoarseness (due to compression of the left reourrent laryngeal nerve, a branch of the vagus)





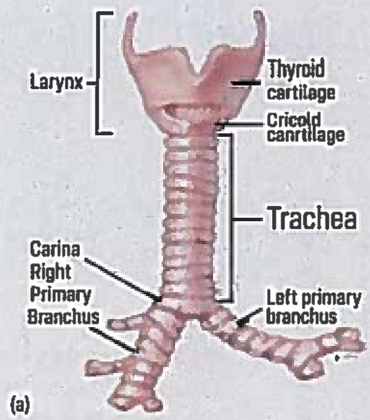
Intercostal Space

- Vessels arrangement:
  - Form above downwards – (**VAN**)
    - **V**ein, **A**rtery then **N**erve
- Neurovascular bundle in chest wall lies between internal and innermost layers.
- Regarding intercostobrachial nerve= 2nd intercostal is sensory.
- Blood supply:
  - Anteriorly:
    - Upto 6th intercostal space = internal thoracic artery
    - Below 6th space= phrenic artery
  - Posteriorly:
    - First 2 intercostal space= superior intercostal
    - 3-9 intercostal space= thoracic aorta



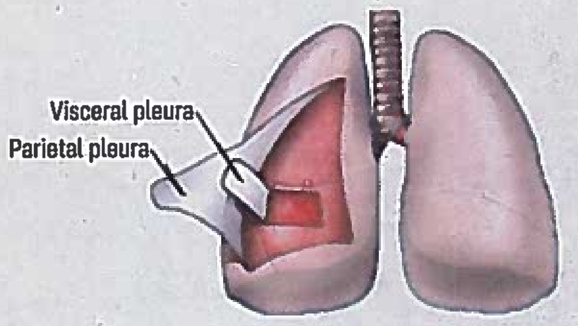
Trachea

- Continuation of larynx
- Begins at lower border of cricoid cartilage (6th cervical vertebrae)
- Terminates in thorax by dividing into right and left bronchi at sternal angle



Pleura

- Parietal pleura (outer layer):
  - Nerve supply:
    - Costal pleura: intercostal nerves
    - Mediastinal pleura: phrenic nerve
    - Diaphragmatic pleura: lower 5 intercostal nerve
  - Parietal pleura is pain sensitive
- Visceral pleura:
  - Nerve supply:
    - Autonomic nerves
    - Insensitive to pain and temperature.



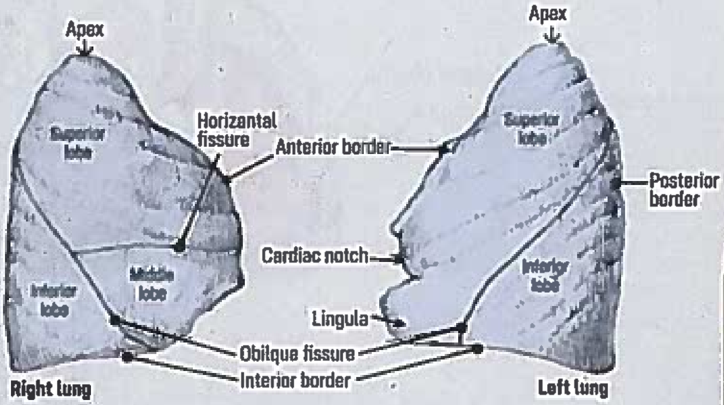
Lungs

Lobes of lung	**Right lung** • Superior lobe • Middle lobe • Inferior lobe	**Left lung** • Superior lobe • Inferior lobe
Fissures of lung	• Oblique fissure: ◦ Runs from inferior border upward and backward across medial and costal surfaces until it cuts the posterior border below the apex • Horizontal fissure: ◦ Present only in right lung ◦ Extends horizontally across costal surface at level of fourth costal cartilage to meet the oblique fissure in midaxillary line	
Bronchopulmonary Segment	• Bronchopulmonary segment is anatomical, functional and surgical unit of lung • Pyramidal in shape with apex towards the lung roots • Contains segmental bronchus, segmental artery, lymph vessels and autonomic nerves • Segmental Vein lies between two adjacent bronchopulmonary segments	
Cardiac notch Segment	• The anterior border of left lung overlaps heart, a notch called the cardiac notch	
Lingual	• Tongue shaped projection of left lung below cardiac notch is called lingual	
Blood supply	• Bronchial arteries → branches of descending thoracic aorta	
Venous drainage	• Drains into azygous vein and Hemiazygous vein	
Nerve supply	• Pulmonary plexus → Sympathetic trunk + parasympathetic fibers from vagus nerve	

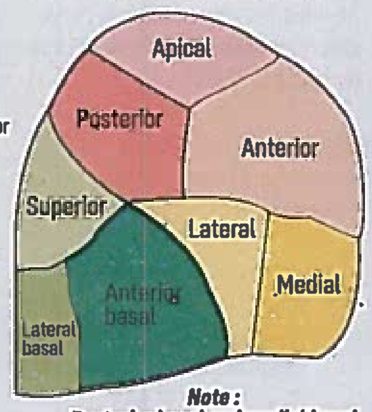
Lung Roots Relations	• Structures which arches over root of lung • Over Left lung root → Aorta • Over Right lung root → Azygous vein • Structures anterior to root of both lungs → Phrenic nerve • Structures posterior to root of both lungs → Vagus nerve • Pulmonary trunk relation with the bronchus at the hilum of the lung-mnemonic is (RALS) → Right Anterior & Left Superior.

NOTE:

- Right lung is a more common site for inhaled foreign bodies
- Because right main stem bronchus is wider, more vertical, and shorter than the left.
- If you aspirate a peanut:
    - While upright—enters basal (posterior) segments of right lower lobe.
    - While supine—enters Apical (superior) segment of right lower lobe. Preferentially on right side.

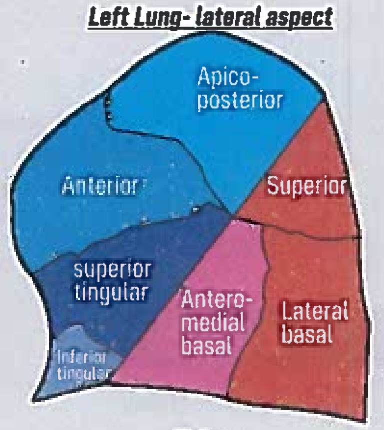


Right Lung- lateral aspect



Note : Posterior basal and medial basal segments are obscured from view

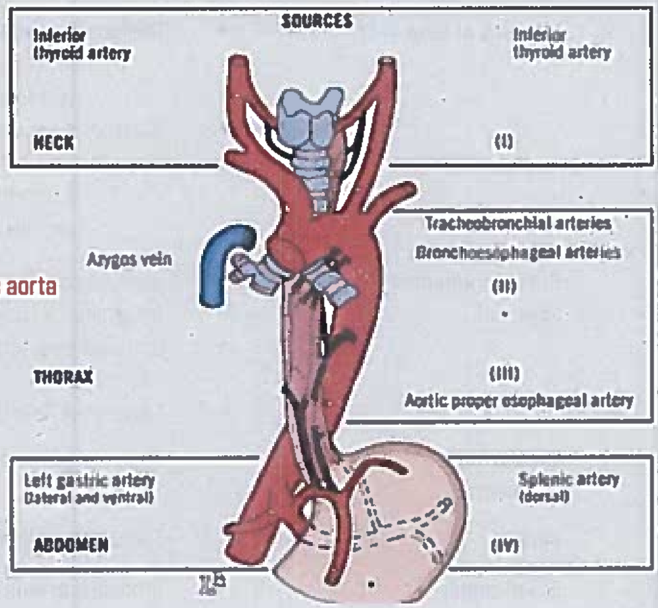
Left Lung- lateral aspect



Note : Posterior basal segment is obscured from view

Esophagus

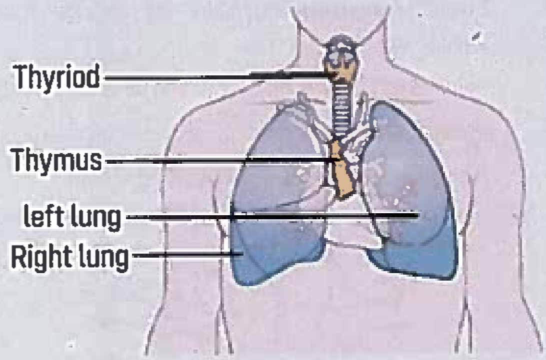
- Three constrictions
    - Where it begins
    - Where it is crossed by left bronchus
    - Where it pierces diaphragm
- Arterial supply:
    - Upper third → Inferior thyroid artery
    - Middle third → Branches from descending thoracic aorta
    - Lower third → Left gastric artery
- Venous drainage:
    - Upper third → Inferior thyroid vein
    - Middle third → Azygous vein
    - Lower third → Left gastric vein



Thymus

- Located in the anterosuperior mediastinum
- Thymus is derived from the Third pharyngeal pouch
- Important source of T-lymphocyte
- Site of T-cell differentiation and maturation
- Flattened bilobed structure b/w sternum and pericardium

- It continues to grow until puberty
- Diseases:
    - Hypoplastic in DiGeorge syndrome and severe combined immunodeficiency (SCID).
    - Thymoma—benign neoplasm of thymus, Associated with myasthenia gravis and superior vena cava syndrome

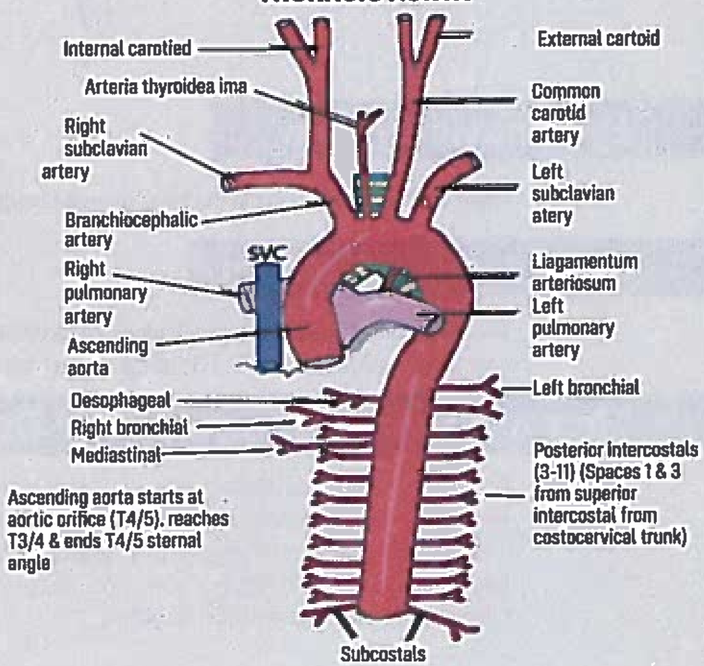


Large Arteries of Thorax

Aorta

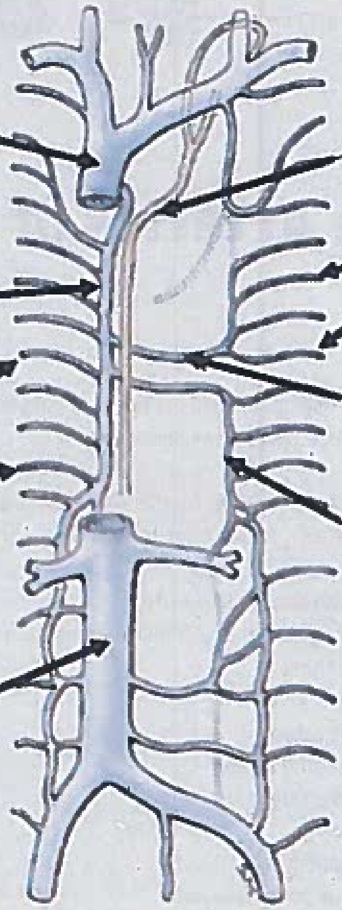
- **Ascending aorta:**
    - Arises from left ventricle ascend to level of sternal angle and becomes continuous with arch of aorta.
    - At its root it possesses three bulges (sinuses of aorta)
    - Branches:
        - Right coronary artery: arises from anterior aortic sinus
        - Left coronary artery: arises from left posterior aortic sinus
- **Arch of aorta:**
    - It becomes continuous with descending aorta
    - The arch is related inferiorly to root of left lung, ligamentum arteriosum, left recurrent laryngeal nerve, bifurcation of pulmonary trunk
    - Branches:
        - Brachiocephalic artery
        - Left common carotid artery
        - Left subclavian artery
- **Descending aorta:**
    - Passes through aortic opening in diaphragm and continue as abdominal aorta
    - Branches:
        - Posterior intercostal arteries
        - Subcostal arteries
        - Esophageal arteries
        - Bronchial arteries

THORACIC AORTA



Large Veins of Thorax

Brachiocephalic vein	• Formed by union of subclavian and internal jugular vein
Superior vena cava	• Formed by union of right and left brachiocephalic vein
Azygous vein	• Union of right ascending lumbar vein and right subcostal vein • It joins superior vena cava
Inferior Hemiazygous vein	• Union of left ascending lumbar and left subcostal vein. It joins azygous vein
Superior Hemiazygous vein	• Union of 4th with 8th intercostal vein, it joins azygous vein
Inferior vena cava	• Formed in abdomen, Opens into right atrium



Lymphatic System

- There are two lymph ducts in the body, the right lymphatic duct and the thoracic duct.

Right Lymphatic Duct

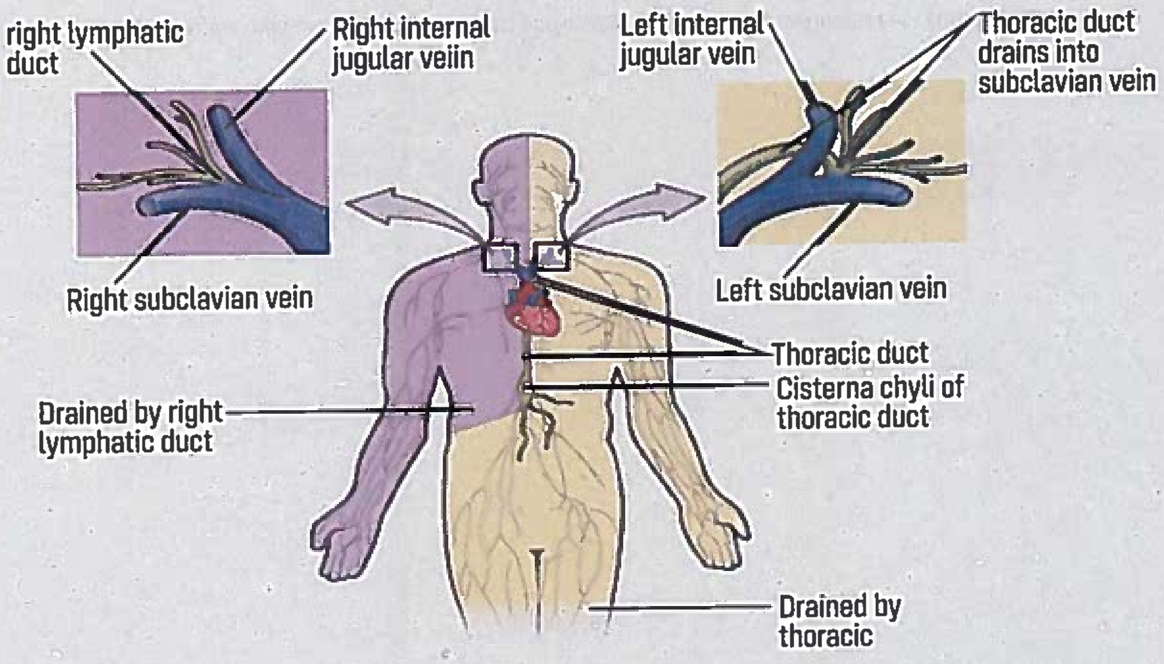
- The right jugular, subclavian, and bronchomediastinal trunks, which drain the right side of the head and neck, the right upper limb, and the right side of the thorax, respectively, may join to form the right lymphatic duct.

Thoracic Duct (Left Lymphatic Duct)

- The thoracic duct is the largest lymphatic vessel of the lymphatic system
- The thoracic duct begins below in the abdomen as a dilated sac, the cisterna chyli.
- It ascends through the aortic opening in the diaphragm,
- The thoracic duct drains lymph into the circulatory system at the left brachiocephalic vein between the left subclavian and left internal jugular veins.

Lymphatic Drainage and Spread

Cervical	• Head and neck
Hilar	• Lungs
Mediastinum	• Trachea and esophagus
Axillary	• Upper limb, breast, skin above umbilicus
Celiac	• Liver, stomach, spleen, pancreas, upper duodenum
Superior mesenteric	• Lower duodenum, jejunum, ileum, colon to splenic flexure
Inferior mesenteric	• Colon from splenic flexure to upper rectum
Internal iliac	• Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), prostate
Para-aortic	• Testes, ovaries, kidneys, uterus
Superficial inguinal	• Anal canal (below pectinate line), skin below umbilicus (except popliteal territory), scrotum
Popliteal	• Dorsolateral foot, posterior calf



Applied Anatomy

Ribs

- Typical ribs: 3rd to 9th
- Atypical ribs: 1st 2nd and 10th, 11th, 12th ribs

Sternum

- Common site for marrow biopsy

Thoracic Outlet Syndrome

- Brachial plexus and subclavian artery and vein closely related to first vertebrae.
- Here the nerve and blood vessels may be compressed between bones.

Right Bronchus

- Wider and more direct than left
- Foreign bodies tends to enter right instead of left

Atrial Septal Defect

- Failure of closure of foramen ovale

Tetralogy Of Fallot

- Mnemonic: **PROVe**
  - **P**ulmonary stenosis
  - **R**ight ventricular hypertrophy
  - **O**verriding of aorta (Aorta originates from right ventricle)
  - **V**entricular septal defect causes blood flow from left to right ventricle
- All four factors cause blood to bypass lungs so blood is not oxygenated

Patent Ductus Arteriosus

- Normally ductus arteriosus closes by end of first month after birth
- Failure of closure results in aortic blood passing into pulmonary artery
- Which then raises the pressure in pulmonary circulation and causes hypertrophy of right ventricle.

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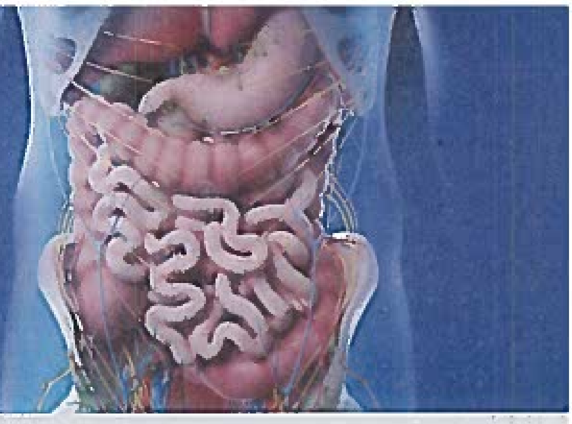


Chapter 4: Abdomen

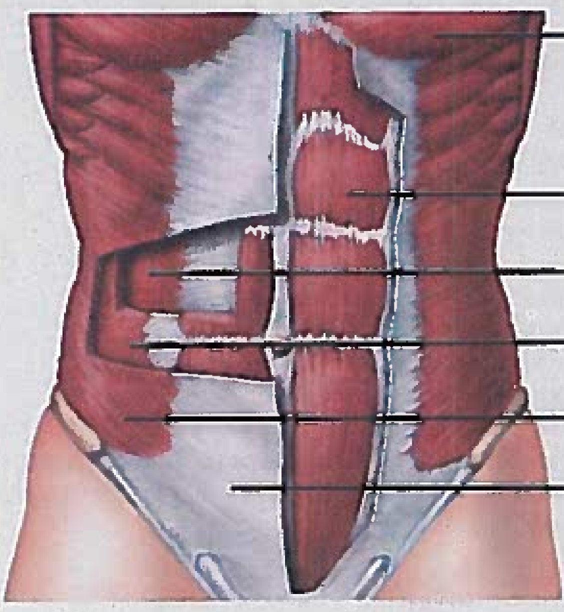
Muscles of Anterior Abdominal Wall

- The anterior abdominal wall is made up of 6 muscles; 4 large and 2 small muscles.
- 4 large muscles are external oblique, internal oblique, transverse abdominus, rectus abdominus
- 2 small muscles, Pyramidalis and cremaster.
- External, internal and transverse each of them ends in aponeurosis, which extends to mid line called linea Alba.
- The rectus abdominus runs on either side of linea Alba.
- Cremaster muscle is derived from lower fibers of internal oblique, supplied by genital branch of Genitofemoral nerve. The muscle is fully developed only in males

Muscle	Origin	Insertion	Nerve Supply
External oblique	Lower eight ribs	Xiphoid process, linea alba, pubic crest, pubic tubercle, iliac crest	Lower six thoracic nerves and iliohypogastric and ilioinguinal nerves (L1)
Internal oblique	Lumbar fascia, iliac crest, lateral two thirds of inguinal ligament	Lower three ribs and costal cartilages, xiphoid process, linea alba, symphysis pubis	Lower six thoracic nerves and iliohypogastric and ilioinguinal nerves (L1)
Transversus	Lower six costal cartilages, lumbar fascia, iliac crest, lateral third of inguinal ligament	Xiphoid process, linea alba, symphysis pubis	Lower six thoracic nerves and iliohypogastric and ilioinguinal nerves (L1)
Rectus abdominis	Symphysis pubis and pubic crest	5th, 6th and 7th costal cartilages and xiphoid process	Lower six thoracic nerves

Muscles of Posterior Abdominal Wall

Muscle	Origin	Insertion	Nerve Supply
Psoas	Transverse processes, bodies, and intervertebral discs of 12th thoracic and five lumbar vertebrae	With iliacus into lesser trochanter of femur	Lumbar plexus
Quadratus lumborum	Iliolumbar ligament, iliac crest, tips of transverse processes of lower lumbar vertebrae	12th rib	Lumbar plexus
Iliacus	Iliac fossa	With psoas into lesser trochanter of femur	Femoral nerve



Pectoralis major
Rectus abdominis
Transversus abdominis
Internal oblique
External oblique
Aponeurosis

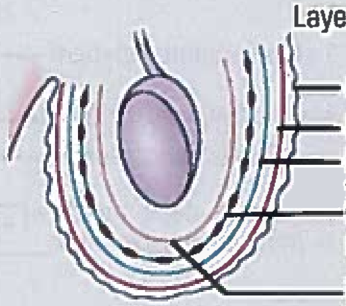
diaphragm
Lateral archute ligament
Quadratus limborum muscle
Psoas minor muscle
Rsoas major muscle
Transversus alxominis muscle
Iliacus muscle
Piriformis Muscle
Coccygeus (ischiococcygeus) Muscle
Rectococcygeus muscle
Inguiinal Ligament (Poupart's)
Lacunar ligament (Gimbernat's)
Levator uni muscle
L1
L2
L3
L4
L5

Inguinal Ligament

- The inguinal ligament is formed by the lower border of the external oblique aponeurosis which is thickened and folded backwards on itself.
- It extends from the anterior superior iliac spine to the pubic tubercle.
- Attachments:
  - Fascia lata (lower border)
  - Internal oblique (lower 2/3)
  - Transversus abdominus (lateral 1/3)
  - Cremaster muscle (middle part)
- Extension:
  - The pectineal part of the inguinal ligament or lacunar ligament is triangular
  - The pectineal ligament or ligament of Cooper
  - The reflected part of the inguinal ligament
  - Conjoint Tendon or Falx Inguinalis:
    - The conjoint tendon is formed by fusion of the internal oblique and of the transversus muscles
    - Attached to the pubic crest and to the medial part of the pectin pubis.
    - The conjoint tendon strengthens the abdominal wall at the site where it is weakened by the superficial inguinal ring.

Scrotum

- The scrotum is a cutaneous bag containing
  - The right and left testes.
  - the epididymis
  - And the lower parts of the spermatic cords.
- Layers of the Scrotum: (**S**ome **D**irty **E**nglishmen **C**alled **It** **T**estis)
  - **S**kin
  - **D**artos muscle
  - The **E**xternal spermatic fascia
  - The **Cre**masteric fascia
  - The **I**nternal spermatic fascia.
  - **T**unica vaginalis.



Testis

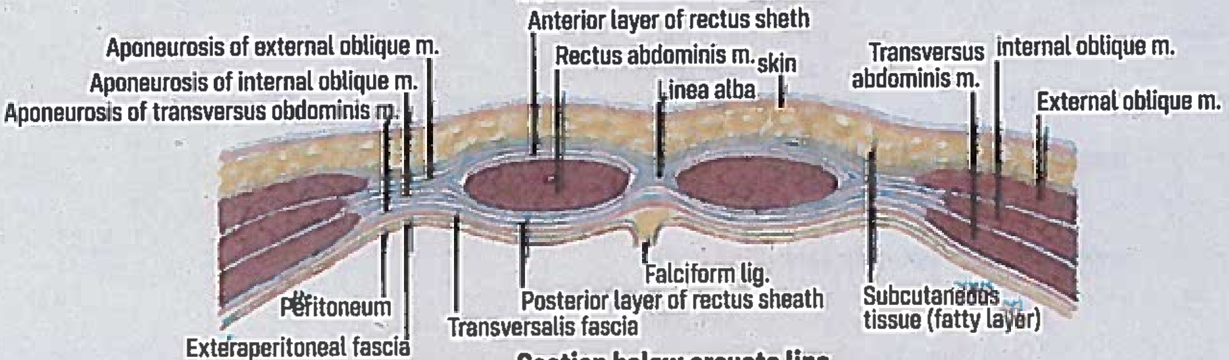
- Paired, ovoid organs responsible for production of spermatozoa and testosterone.
- Coverings of the Testis: (from outwards to inside)
  - Tunica Vaginalis
  - Tunica Albuginea
  - Tunica vasculosa
- Blood supply → testicular artery (branch of abdominal aorta)
- Venous drainage
  - Right testicular vein drains into inferior vena cava
  - Left testicular vein in to left renal vein
- Applied anatomy:
  - Because the left spermatic vein enters the left renal vein at a 90° angle, flow is less laminar on left than on right
  - Left venous pressure > right venous pressure → varicocele more common on the left.

Rectus Sheath

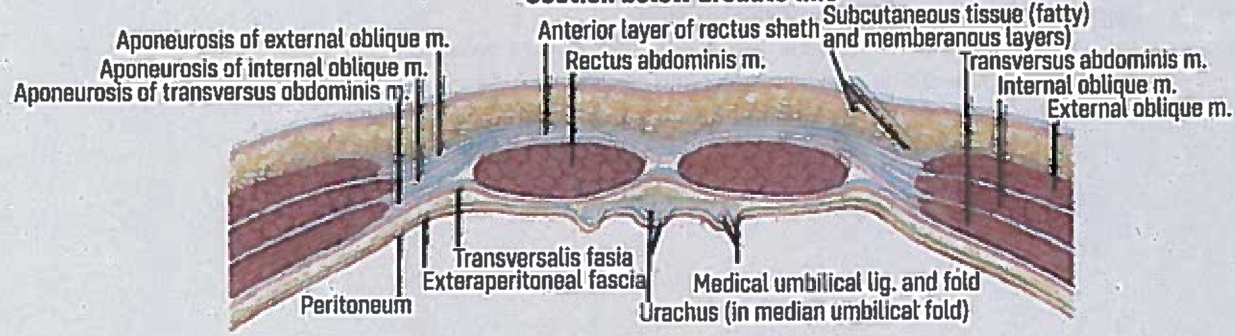
- This is an aponeurotic sheath (of external, internal, transverse) covering the rectus abdominis muscle.
- It has two walls, anterior and posterior

Features:	Anterior wall: • It is complete, covering the muscle from end to end. • It is firmly adherent to the tendinous intersections of the rectus muscle Posterior wall: • It is incomplete, being deficient above the costal margin and below the arcuate line. • It is free from the rectus muscle	
Contents	Muscles→ The rectus abdominis and The Pyramidalis. Arteries → Superior and inferior epigastric artery Veins→ The superior and inferior epigastric vein Nerves→Lower six thoracic nerves	
Formation	**Above the costal margin**	Anterior wall →External oblique aponeurosis. Posterior wall →It is deficient
	Between costal margin and arcuate line	Anterior wall: • External oblique aponeurosis. • Anterior lamina of the aponeurosis of the internal oblique. Posterior wall: • Posterior lamina of the aponeurosis of the internal oblique • Aponeurosis of the transversus muscle
	Below the arcuate line	Anterior wall: • Aponeurosis of all the three flat muscles of the abdomen. • The aponeurosis of the transversus and the internal oblique are fused, but the external oblique aponeurosis remains separate. Posterior wall: • It is deficient. The rectus muscle rests on the fascia transversalis.

Section above arcuate line



Section below arcuate line



Inguinal Hernia

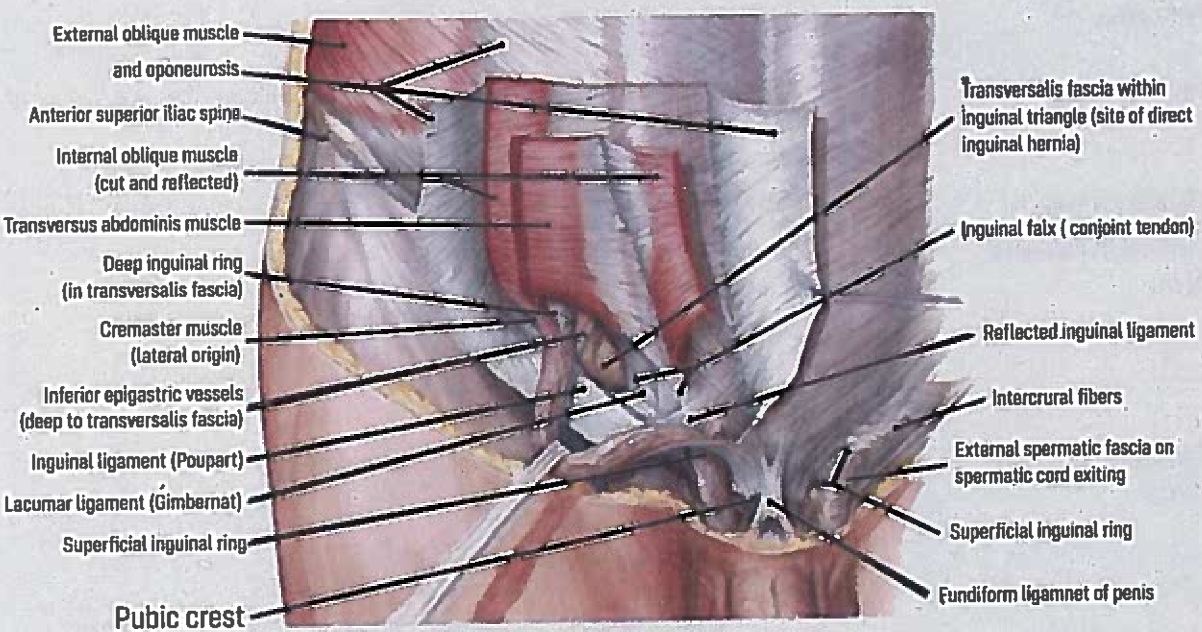
- Abnormal protrusion of abdominal contents (greater omentum and intestines) into the inguinal canal is known as inguinal hernia.
- Direct inguinal hernia:
  - When the contents of the hernia enter the inguinal canal, not through the deep ring, but through the posterior wall (lying medial to the inferior epigastric artery).
- Indirect inguinal hernia:
  - When the contents of the hernia enter the inguinal canal by passing through the deep inguinal ring (lying lateral to the inferior epigastric artery) the hernia is said to be indirect.
- Hesselbach's triangle:
  - Boundaries:
    - Medially: lateral border of the rectus abdominis
    - Laterally: inferior epigastric artery
    - Below: inguinal ligament.
    - Direct hernia occurs through Hesselbach's triangle

Inguinal Canal

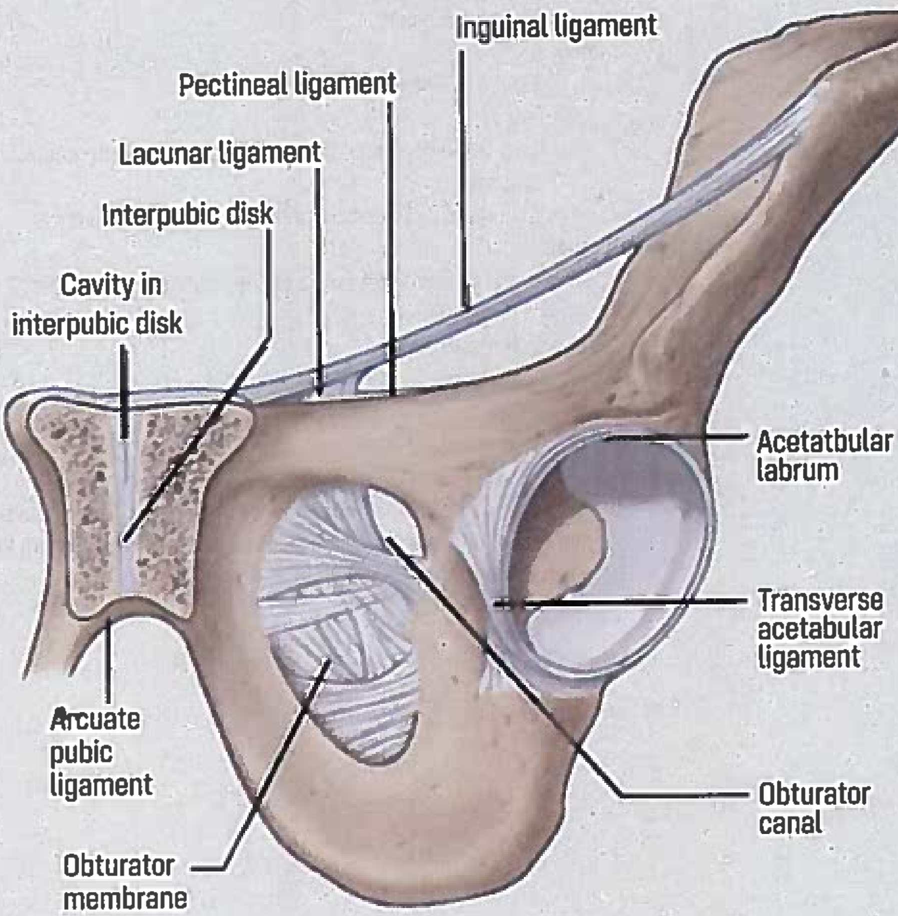
- This is an oblique passage in the lower part of the anterior abdominal wall, situated just above the medial half of the inguinal ligament.
- The inguinal canal extends from the deep inguinal ring to the superficial inguinal ring.
- **The Deep Inguinal Ring:**
  - Is an oval opening in the fascia transversalis
  - Situated 1.2 cm above the midinguinal point, and immediately lateral to the stem of the inferior epigastric artery.
- **The Superficial Inguinal Ring:**
  - Is a triangular gap in the external oblique aponeurosis
  - It lies above and medial to the pubic tubercle
- Boundaries:

Anterior wall	• External oblique aponeurosis along entire length. • In its lateral one-third: The fleshy fibres of the internal oblique muscle
Posterior wall	• The fascia transversalis in its whole extent. • In its medial two-thirds → the conjoint tendon.
Roof	• It is formed by the arched fibres of the internal oblique and transversus abdominis muscles
Floor	• Inguinal ligament • Lacunar ligament (medial end)

- **Structures Passing through the Canal**
  - The spermatic cord in males, or the round ligament of the uterus in females.
  - The ilioinguinal nerve.
- **Constituents of the Spermatic Cord: (RULE OF 3):**
  - 3 Arteries: Testicular, Cremasteric, Artery to ductus deferens
  - 3 Nerves: Genital branch of the genitofemoral, Cremasteric, autonomics.
  - 3 Other things: Ductus deferens, Pampiniform plexus, Lymphatics
- **Coverings of Spermatic Cord (From within outwards)**
  - The internal spermatic fascia (derived from the fascia transversalis)
  - The cremasteric (derived from the internal oblique)
  - The external spermatic fascia (derived from the external oblique aponeurosis)



Anterior view



Peritoneum

Two Layers

- An outer or parietal layer
- An inner or visceral layer.

Parietal Peritoneum

- It lines the inner surface of the abdominal and pelvic walls and the lower surface of the diaphragm.
- Because of the somatic innervation, parietal peritoneum is pain sensitive

Visceral Peritoneum

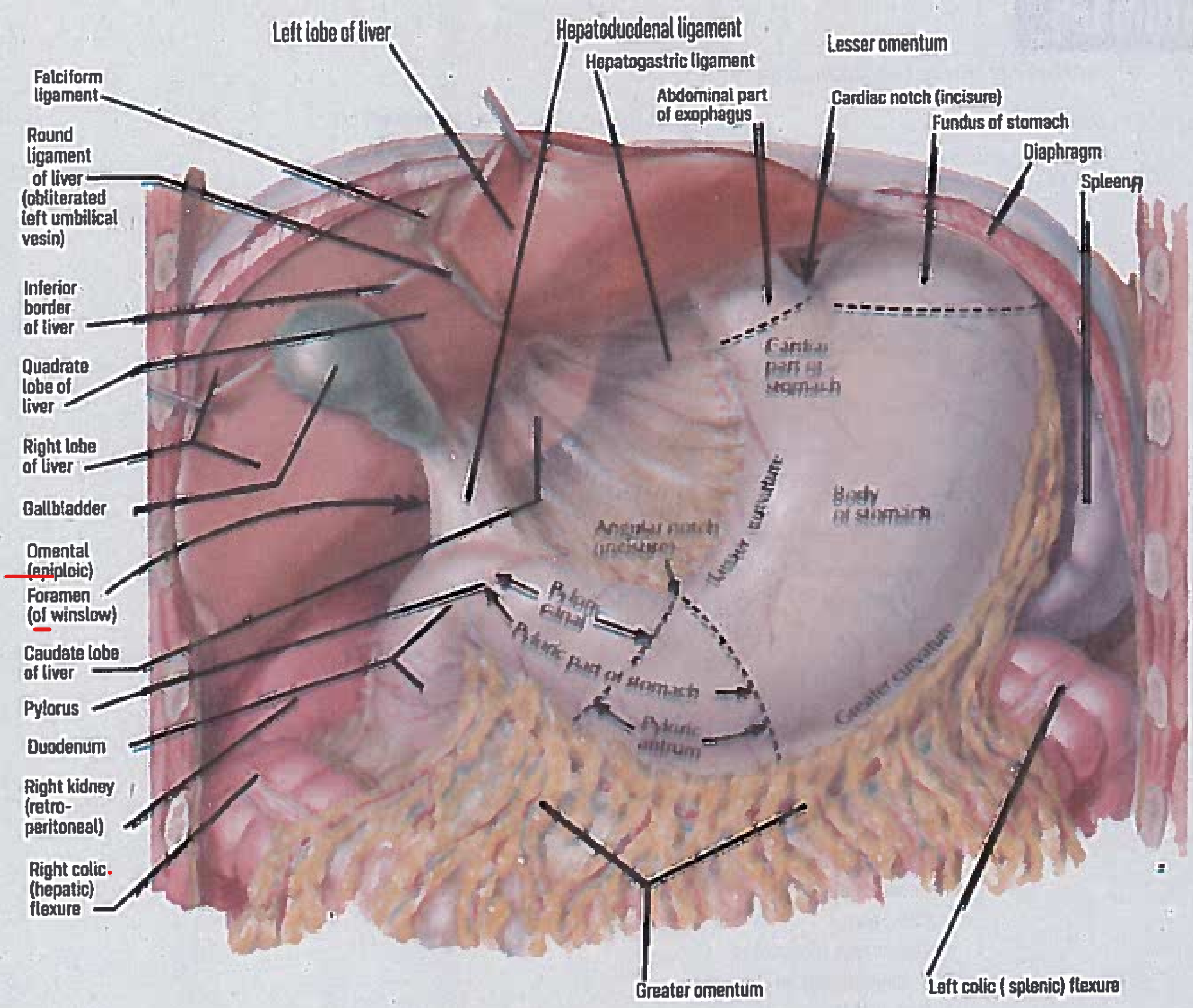
- It lines the outer surface of the viscera.

Divisions Of Peritoneal Cavity

- The peritoneal cavity is divided broadly into two parts
  - Greater sac: main larger part
  - Lesser sac: smaller part, situated behind the stomach, the lesser omentum and the liver.
  - The two sacs communicate with each other through the epiploic foramen or foramen of Winslow or opening into the lesser sac

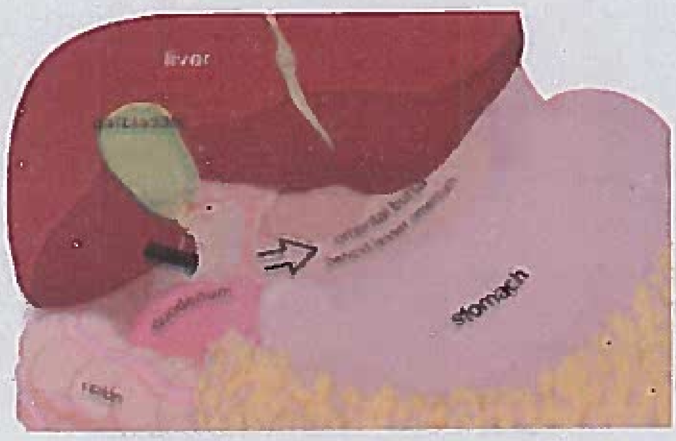
Divisions Of Peritoneal Cavity

- Organs within abdomen are suspended by peritoneal folds of peritoneum.
  - Mesentry (intestine)
  - Omentum (stomach)
  - Peritoneal ligaments
- **Greater omentum:**
  - This is a large fold of peritoneum which hangs down from the greater curvature of the stomach like an apron and covers the loops of intestines to a varying extent.
  - Attachments:
    - From greater curvature of the stomach
    - Folded back on itself and is attached to inferior border of transverse colon.
  - Contents:
    - Right and left gastroepiploic vessels
    - Fat
    - Gastrosplenic ligament: From hilus of spleen to greater curvature of stomach
    - Lienorenal ligament: From hilus of spleen to kidney
- **Lesser omentum:**
  - Extends from the lesser curvature of the stomach and the first 2 cm of the duodenum to the liver.
  - Contents: (Portal triad)
    - Portal vein
    - Bile duct
    - Hepatic artery
- **Mesenteries:**
  - The mesentery of the small intestine (or mesentery proper) is a broad, fan-shaped fold of peritoneum which suspends the coils of jejunum and ileum from the posterior abdominal wall



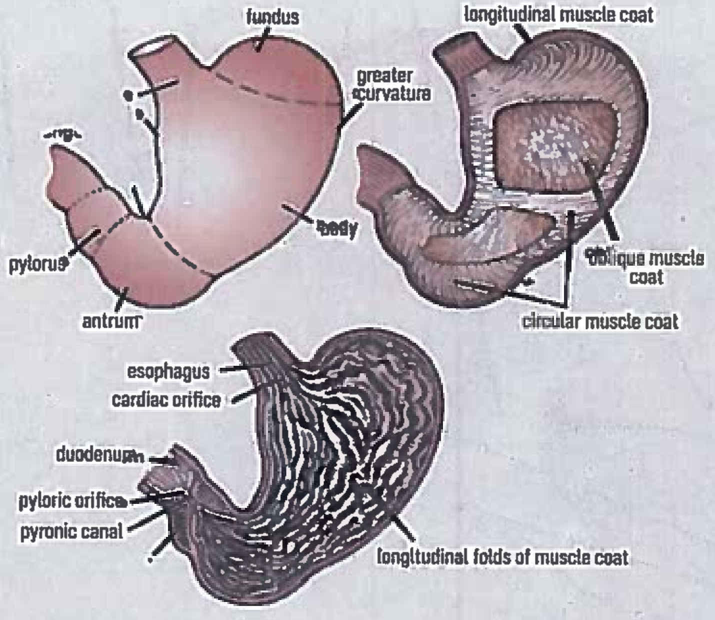
Epiploic foramen

- This is a vertical slit-like opening through which the lesser sac communicates with the greater sac
- Boundaries:
  - Anteriorly: Right free margin of the lesser omentum
  - Posteriorly: The inferior vena cava.
  - Superiorly: Caudate process of the liver.
  - Inferiorly: First part of the duodenum



Stomach

- Divided into fundus, body and pylorus



- **Visceral Relations**
  - Anterior surface:
    - Liver, diaphragm and anterior abdominal wall
  - Posterior surface: (stomach bed)—all separated by lesser sac
    - The diaphragm
    - Left kidney
    - Suprarenal gland
    - Pancreas
    - Transverse mesocolon
    - Splenic flexure of the colon
    - Splenic artery.
- **Blood supply:**
  - Left gastric artery, a branch of the coeliac trunk
  - Right gastric artery, a branch of the common hepatic
  - Right gastroepiploic artery, a branch of the gastroduodenal
  - Left gastroepiploic artery, a branch of the splenic
  - 5 to 7 short gastric arteries, which are also branches of the splenic artery
- **Venous drainage** into portal, superior mesenteric vein and splenic vein.
- **Nerve supply:**
  - Sympathetic: celiac plexus
  - Parasympathetic: vagus nerve

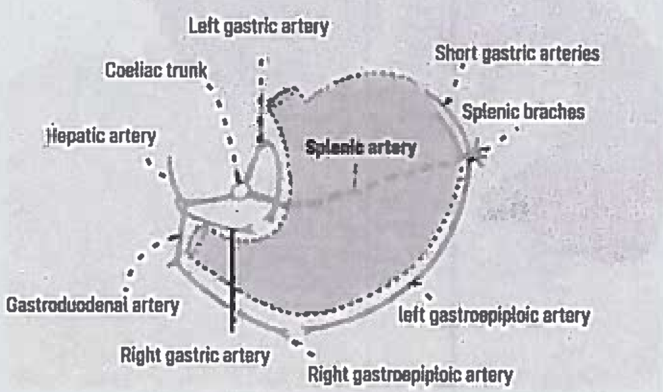


Fig. 19.6: Arteries supplying the stomach.

Small Intestine

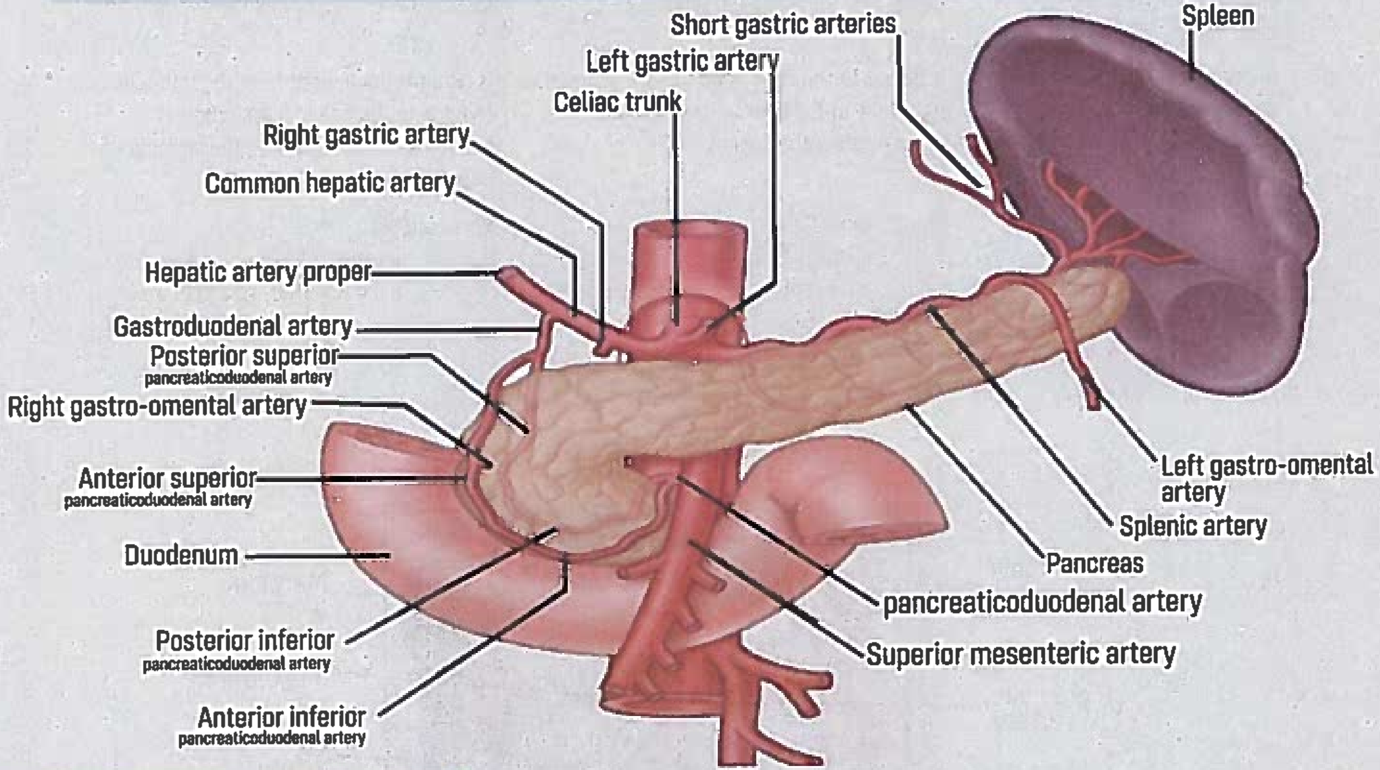
Duodenum

- C-shaped
- It extends from the pylorus to the duodenojejunal flexure.
- Divided into four parts

1st part (2 inches)	• Upto transpyloric plane at level of 1st lumbar vertebrae L1
2nd part (3 inches)	• Receives bile and pancreatic duct that unite and opens into major duodenal papilla • Accessory pancreatic duct opens into minor duodenal papilla
3rd part (4 inches)	• It is retroperitoneal and fixed
4th part (1 inches) Right crus	• Runs toward duodenojejunal flexure • The flexure is held in position by ligament of treitz, which is attached to right crus of diaphragm

- Blood supply:

- Upper half of duodenum: superior pancraticoduodenal artery (branch of gastroduodenal artery) →drains into portal vein
- Lower half of duodenum: inferior pancraticoduodenal artery (branch of superior mesenteric artery) →drains into mesenteric vein



Jejunum and ileum

- Jejunum begins at duodenojejunal flexure, thicked walled and redder in colour than ileum
- Coils of ileum occupy lower right part of abdominal cavity and ends at illeocecal junction.
- Blood supply:
  - Branches of superior mesenteric arteries anastomose with one another
  - Veins drain into mesenteric vein.
- Nerve supply: sympathetic and vagus nerve arises from mesenteric plexus

Large Intestine

- The large intestine extends from the ileum to the anus.
- It is divided into the cecum, appendix, ascending colon, transverse colon, descending colon, sigmoid colon, rectum and anal canal

Cecum

- It is a blind-ended pouch that is situated in the right iliac fossa.
- Joined with ileum and ascending colon.
- Blood supply→ superior mesenteric artery (anterior and post. Cecal arteries)

2 cm
1

Appendix

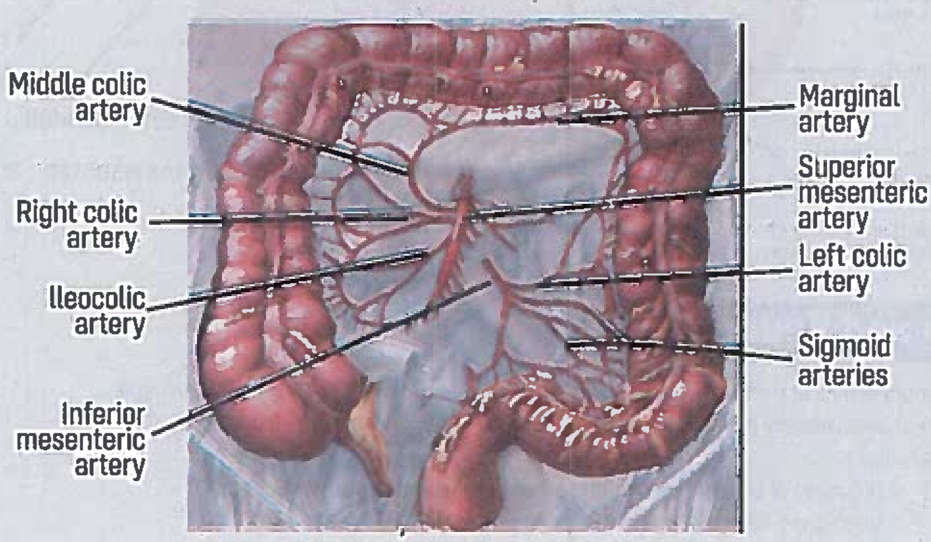
- Attached to the posteromedial surface of the cecum about 1 in. (2.5 cm) below the ileocecal junction
- Blood supply → The appendicular artery is a branch of the posterior cecal artery

Note In Appendectomy:

- Nerve damaged = Illiohypogastric nerve (common)
- Artery damaged = deep circumflex iliac artery

Colon

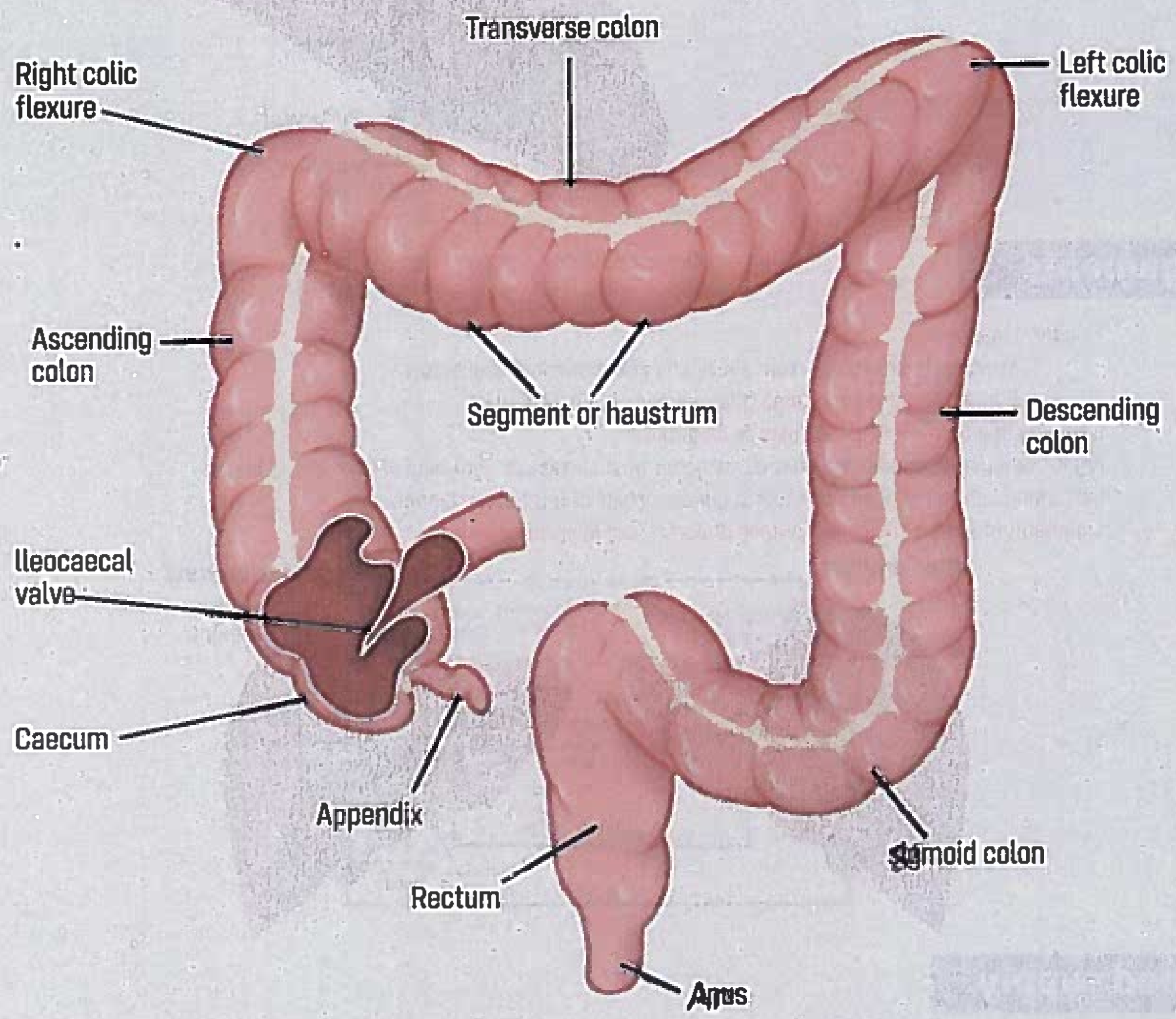
Ascending colon	Transverse colon	Descending colon
Lies in the right lower quadrant.	Occupying the umbilical region.	Lies in the left upper and lower quadrants
It extends upward From the cecum to right colic flexure, and becomes continuous with the transverse colon.	It begins at the right colic flexure below the right lobe of the liver to the left colic flexure below the spleen	It extends downward from the left colic flexure, to the pelvic brim, where it becomes continuous with the sigmoid colon
Blood supply • Superior mesenteric artery (ileocolic and right colic branches)	Blood supply • Proximal 2/3rd → superior mesenteric artery (middle colic artery). • Distal 1/3rd → Inferior mesenteric artery (left colic artery)	Blood supply • inferior mesenteric artery (left colic and the sigmoid branches)



Differences between Small Intestine and Large Intestine

Features	Small Intestine	Large Intestine
Mobility	• Small intestine (with the exception of the duodenum) • is mobile,	• Whereas the ascending and descending parts of the colon are fixed
Taenia coli (longitudinal muscle collected into 3 bands)	• Absent	• Present
Appendices epiploicae (fatty tags)	• Absent	• Present
Sacculations	• Absent	• Present
Villi	• Present	• Absent
Peyer's patches (Aggregations of lymphoid tissue)	• Present in ileum	• Absent

Fig 1. **Anatomy of the large intestine**

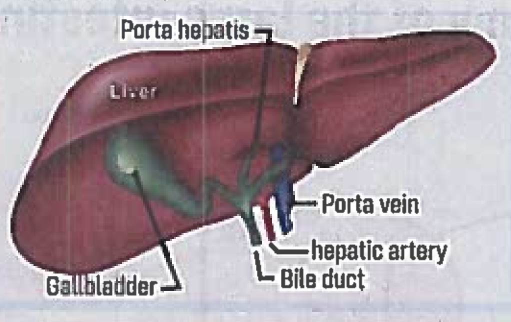


Liver

- Largest organ in body
- Liver is divided into right and left lobe by falciform ligament.
- Right lobe is further divided into caudate (above) and quadrate lobe (below) by presence of gall bladder, fissure for ligamentum teres, inferior vena cava, and ligamentum venosum
- Functionally Quadrate and Caudate lobes are part of left lobe as they receives left branches of hepatic artery and portal vein.

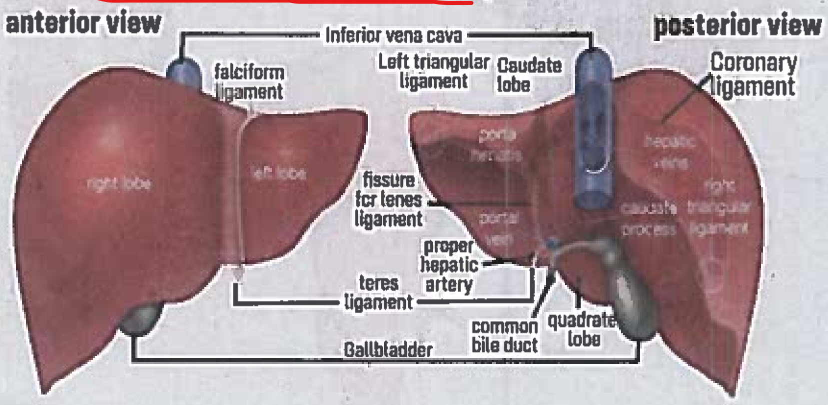
Porta Hepatis: (Hilus Of Liver)

Location	Found on postero inferior surface Lies b/w quadrate lobe below and caudate lobe above. Devoid of peritoneum. Margin of porta hepatis provides attachment to lesser omentum
Contents	Order of structures in the porta hepatis from anterior to posterior is (DAVE) • Ducts (right and left hepatic duct branches) • Arteries (right and left hepatic artery branches) • Vein (portal vein) • Epiploic foramen (of Winslow)



Ligaments

- Falciform ligament:
  - Attaches liver to diaphragm above and ant abdominal wall below
  - Contains ligamentum teres (the remains of umbilical vein)
- Coronary ligament → Attaches liver to diaphragm
- Right triangular ligament → V shaped, attaches post surface of right lobe of liver to diaphragm
- Left triangular ligament → Connects superior surface of left lobe to diaphragm.
- Ligamentum teres → Joins left branch of portal vein in porta hepatis



Blood supply

- Hepatic artery (20%), Portal vein (80%)

Venous drainage

- Interlobar veins→ join to form sublobar veins→these in turn unite to form hepatic veins drain into inferior vena

Lymphatic drainage

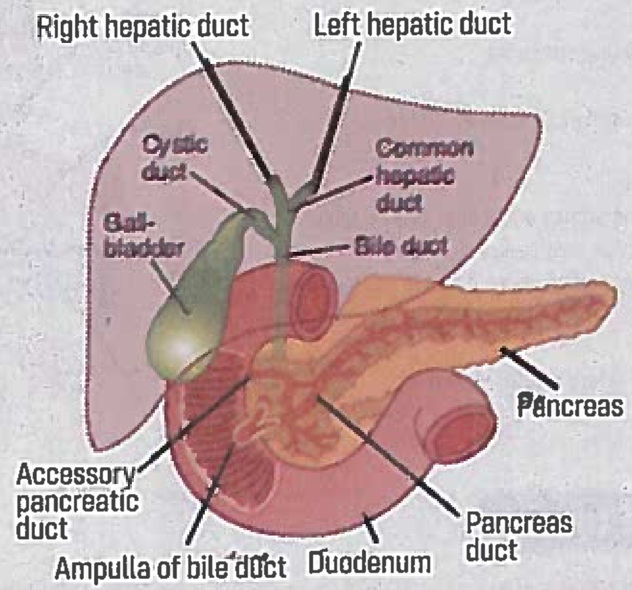
→celiac lymph nodes

Biliary apparatus

- Right and left hepatic ducts emerge from right and left lobe of liver
- Unite to form common hepatic duct
- Joined on right side by cystic duct to form bile duct.

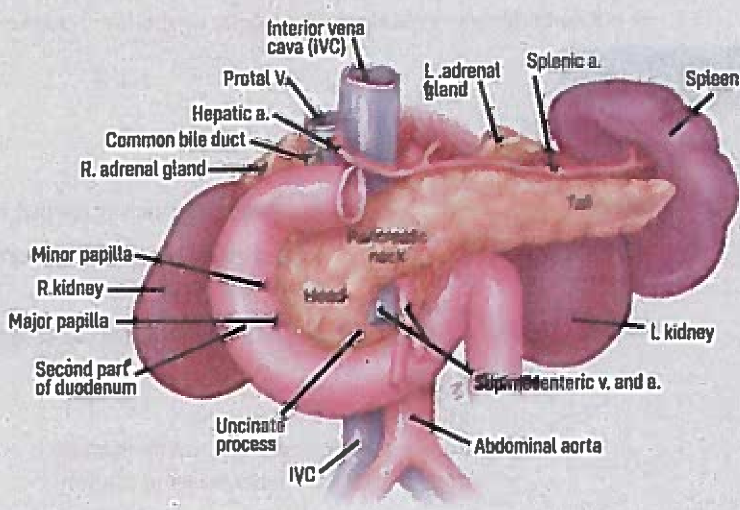
Gall bladder

- Pear shaped organ
- Divided into fundus body and neck
- It stores and concentrate bile by absorbing water
- Blood supply:
  - Cystic artery →branch of right hepatic artery
  - Venous drainage into portal vein
- Lymph drainage:
  - Cystic →hepatic nodes →finally into celiac nodes.



Pancreas

- Exocrine and endocrine gland
- **Divided into**
  - Head: disc shaped and has a process called uncinate process
  - Neck: constricted portion
  - Body: triangular
  - Tail: lies in Lienorenal ligament
- **Pancreas relations**



Head of Pancreas	• Anteriorly → Transverse colon, gastroduodenal artery • Posteriorly → IVC
Neck:	• Posteriorly → termination of Superior mesenteric vein and beginning of portal vein
Uncinate process	• Anteriorly → Superior mesenteric vessels • Posteriorly → Aorta

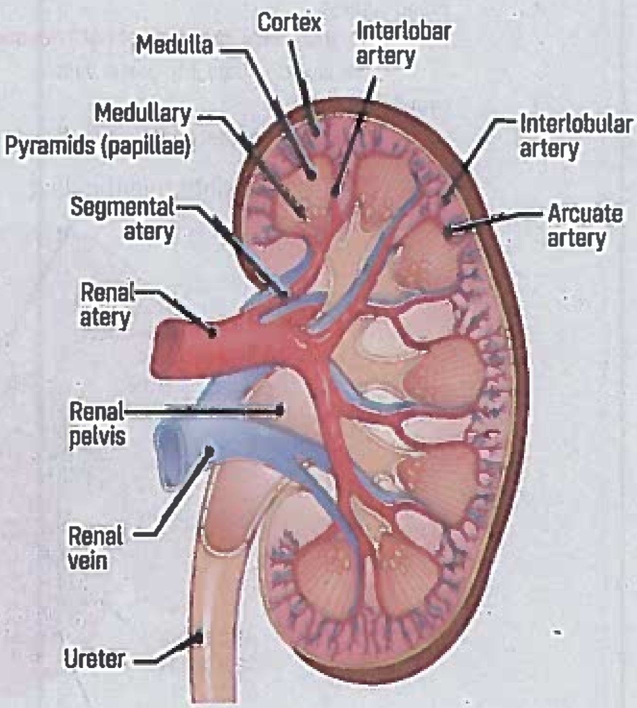
- **Blood supply:**
  - Splenic artery
  - Sup and inf. pancreaticoduodenal arteries.
- **Venous drainage:**
  - Portal vein

Spleen

- Largest single mass of lymphoid tissue.
- Gastrosplenic ligament: b/w stomach and spleen
- Splenicorenal ligament: Spleen with left kidney
- Blood supply: Splenic artery

Kidneys

- Right kidney is slightly lower than left because of liver
- On medial concave border of each kidney is hilus, which transmits renal pelvis, renal artery and renal vein
- Structure:
  - Outer cortex and inner medulla
  - Medulla:
    - Composed of 12 renal pyramids
  - Cortex:
    - 2 parts
    - Cortical arches or cortical lobules which form caps over bases of pyramids
    - renal columns, which dip in b/w pyramids
- Arterial supply:
  - Renal Artery
  - Accessory renal artery (30%) individuals



Note: Renal Blood Flow

Renal artery → segmental artery interlobar artery → arcuate artery → interlobular artery → afferent arteriole → glomerulus → efferent arteriole → vasa recta/peritubular capillaries → venous outflow

Gut

- **Derivatives of Gut**

Foregut	Esophagus, stomach, upper part of duodenum upto opening of common bile duct
Midgut	Rest of duodenum, jejunum, ileum, appendix, caecum, ascending colon, and right 2/3rd of transverse colon
Hindgut	Left 1/3rd of transverse colon, descending colon, proximal upper part of rectum

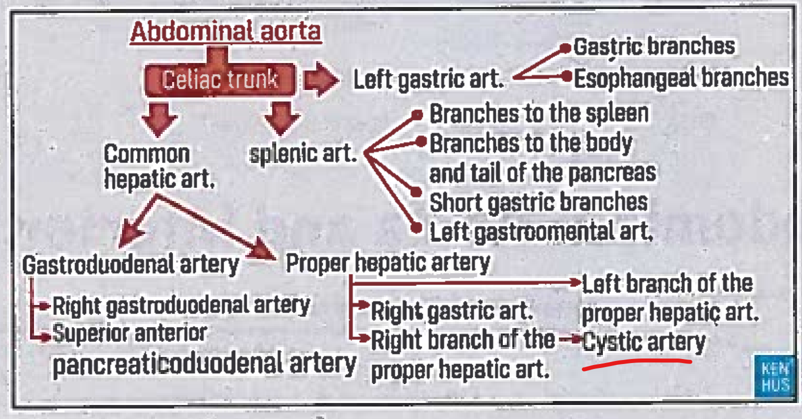
- **Arteries of Gut**
  - Artery of foregut: celiac trunk
  - Artery of midgut: superior mesenteric artery
  - Artery of hindgut: inferior mesenteric artery

Large Vessels of Abdomen

abdominal aorta

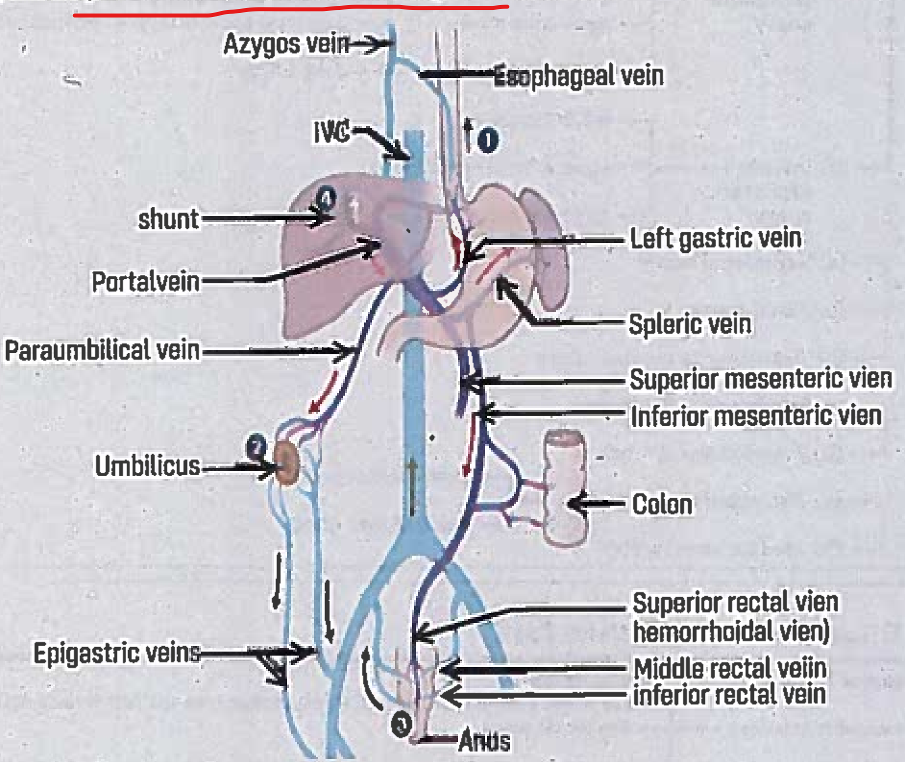
Celiac trunk

- Arises from front of abdominal aorta
- Three terminal branches; left gastric, splenic artery and common hepatic artery.
- Fig shows their branches



Portal vein

- Formed by union of splenic vein and superior mesenteric vein behind the neck of the pancreas
- Portal vein is a large vein which collects blood from; the abdominal part of the alimentary tract, Gall bladder, Pancreas, Spleen and conveys it to the liver.
- In the liver, the portal vein breaks up into sinusoids which are drained by the hepatic veins to the inferior vena cava
- It is called the portal vein because its main tributary, the superior mesenteric vein, begins in one set of capillaries (in the gut) and the portal vein ends in another set of capillaries in the liver.



Port-Caval Anastomosis:

- Under normal conditions, the portal venous blood traverses the liver and drains into the inferior vena cava of the systemic venous circulation by way of the hepatic veins. This is the direct route.
- However, other, smaller communications exist between the portal and systemic systems, and they become important when the direct route becomes blocked.
- These communications are as follows

Site of Anastomosis	Clinical Sign	Portal ↔ Systemic
Umbilicus	Caput medusa (the veins around the umbilicus enlarge)	Paraumbilical ↔ small epigastric veins of the anterior abdominal wall.
Lower end of oesophagus	Esophageal varices	left gastric vein ↔ azygous
Rectum	Anorectal varices	superior rectal vein ↔ middle and inferior rectal veins

Abdominal Aorta and Inferior Vena Cava Summary

Branches of Abdominal Aorta

- 1. Three anterior visceral branches
  - (a) Celiac artery (trunk)
    - left gastric artery
    - splenic artery
      - short gastric arteries (6)
      - splenic arteries (6)
      - left gastroepiploic artery
    - hepatic artery
      - cystic artery
      - right gastric artery
      - gastroduodenal artery
        - right gastroepiploic artery
        - superior pancreatico-duodenal artery
      - right hepatic artery
      - left hepatic artery
  - (b) Superior mesenteric artery
    - jejunal and ileal arteries
    - inferior pancreaticoduodenal artery
    - middle colic artery
    - right colic artery
    - ileocolic artery
      - anterior cecal artery
      - posterior cecal artery—appendicular artery
      - ileal artery
      - colic artery
  - (c) Inferior mesenteric artery
    - left colic artery
    - sigmoid arteries (2 or 3)
    - superior rectal artery
- 2. Three lateral visceral branches
  - (a) Suprarenal artery
  - (b) Renal artery
  - (c) Testicular or ovarian artery
- 3. Five lateral abdominal wall branches
  - (a) Inferior phrenic artery
  - (b) Four lumbar arteries
- 4. Three terminal branches
  - (a) Two common iliac arteries
    - external iliac artery
    - internal iliac artery
  - (b) Median sacral artery

Tributaries of Inferior Vena Cava

- 1. Two anterior visceral tributaries—the hepatic veins
- 2. Three lateral visceral tributaries
  - (a) Right suprarenal vein (the left drains into the left renal vein)
  - (b) Renal veins
  - (c) Right testicular or ovarian vein (the left drains into the left renal vein)
- 3. Five lateral abdominal wall tributaries
  - (a) Inferior phrenic vein
  - (b) Four lumbar veins
- 4. Three tributaries of origin
  - (a) Two common iliac veins
    - external iliac vein
    - internal iliac vein
  - (b) Median sacral vein

Applied Anatomy

Meckel's Diverticulum

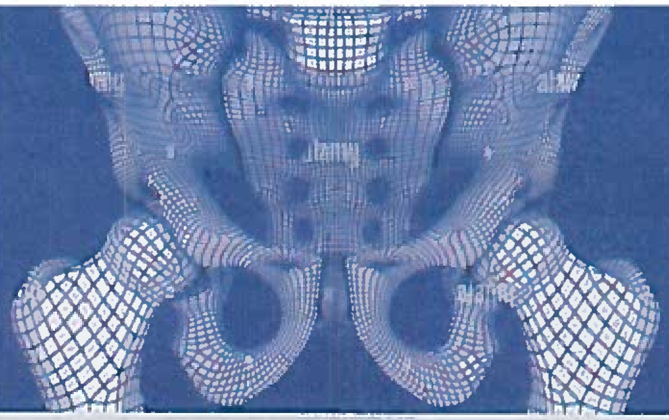
- Meckel's diverticulum, a congenital anomaly, represents a persistent portion of the vitellointestinal duct.
- Rule of **2** for Meckel's diverticulum
  - Occur in **2%** population
  - **2** inches long
  - 2 feet away from ileocecal valve
  - **2%** becomes symptomatic

Superior Mesenteric Artery Syndrome

- Characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when transverse (third) portion of duodenum is compressed between SMA and aorta.
- Typically occurs in conditions associated with diminished mesenteric fat (e.g., low body weight/malnutrition

Drainage Tube

- Cholecystectomy → sub hepatic
- Pancreatitis → lesser sac
- Laparotomy → Rt paracolic



Chapter 5: Pelvis And Perineum

Bones of Pelvis

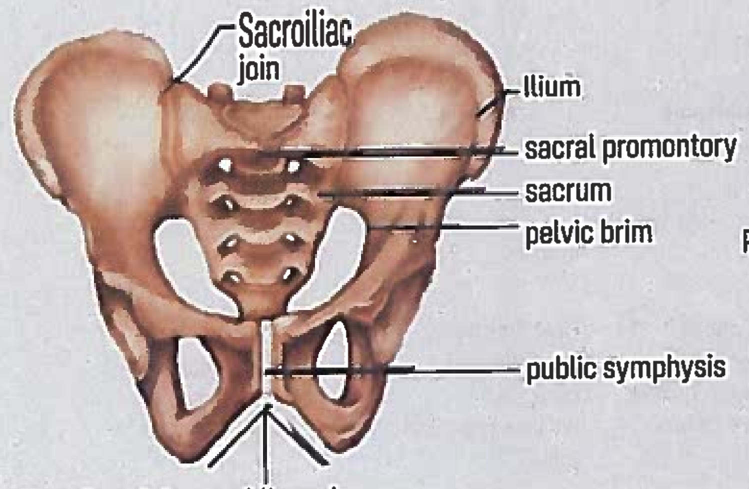
Pelvis

Formed By	• Four bones
	  ◦ 2 hip bones, sacrum and coccyx
	• Four joints
	  ◦ 2 sacroiliac joints (between sacrum and iliac bones)
	  ◦ Pubic symphysis (between two pubic bones)
	  ◦ Sacrococcygeal joint (between sacrum and coccyx)

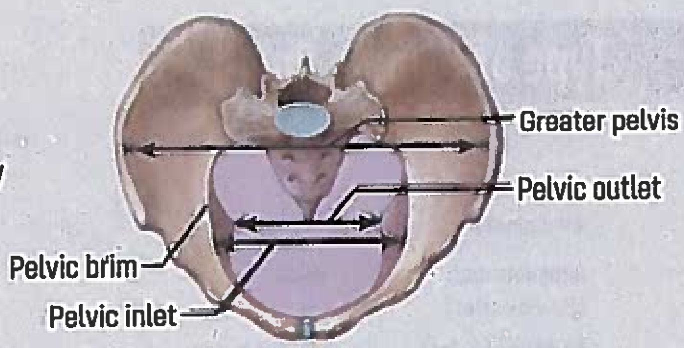
Articulation	• Anteriorly:
	  ◦ Two hip bones articulate with each other
	• Posteriorly:
	  ◦ Sacrum

Pelvic Brim S1	• Posteriorly:
	  ◦ Formed by the sacral promontory (anterior and Upper margin of the first sacral vertebra)
	• Anteriorly:
	  ◦ Symphysis pubis
	• Laterally
	  ◦ Iliopectineal lines (a line that runs downward and forward around the inner surface of the ileum)

True And False Pelvis	• True pelvis:
	  ◦ Below the brim is the true pelvis.
	  ◦ Pelvic Inlet:
	    ▪ Anteriorly → symphysis pubis
	    ▪ Laterally → iliopectineal lines
	    ▪ Posteriorly → sacral promontory
	  ◦ Pelvic outlet
	    ▪ Anteriorly → pubic arch
	    ▪ Laterally → ischial tuberosities
	    ▪ Posteriorly → coccyx.
	• False pelvis:
	  ◦ Above the brim is the false pelvis, which forms part of the abdominal cavity.



a.Female pelvis



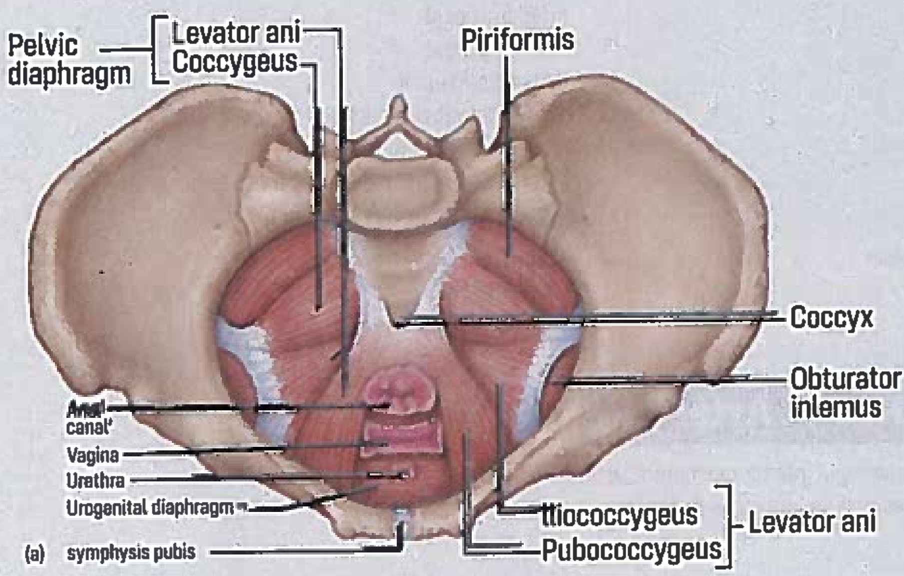
a Superior view showing the pelvic brim and pelvic inlet of a male

Pelvis

	Male Pelvis	Female Pelvis
False Pelvis	Shallow	Deep
Pelvic Inlet	Heart shaped	Oval
Pelvic Outlet	Comparatively smaller	Larger
Subpubic Angle	<90	>90

Walls of Pelvis

Anterior Pelvic Wall	• Shallowest, formed by pubic bones body, pubic rami, and symphysis pubis
Posterior Pelvic Wall	• Formed by sacrum, coccyx, and Piriformis muscle
Lateral Pelvic Wall	• Formed by hip bone, sacrotuberous, Sacrospinous ligaments and obturator internus muscle
Inferior Pelvic Wall (Pelvic Floor)	• Formed by pelvic diaphragm • Pelvic diaphragm formed by • Levator ani • Coccygeal muscle • Pelvic fascia covering these muscles



Type of Female Pelvis

	Gynecoid	Anthropoid	Android	Platypelloid
AP diameter		Wide		Narrow
Subpubic arch (Pelvic outlet)	Wide		Narrow	Wide
Additional points	Most common overall Most favorable for delivery	Narrow ischial spines Much more common in black women	Male type pelvis Pelvic brim is triangular Prominent ischial spines	Pelvic brim is transverse kidney shape Flattened gynecoid shape

Arteries of Pelvis

External Iliac Artery

- Terminal branch of common iliac artery
- Begins in front of sacroiliac joint.
- Runs along the medial border of the psoas muscle
- Ends by passing under inguinal ligament and becomes femoral artery
- Branches:
  - inferior epigastric
  - deep circumflex iliac branches

Internal iliac artery

- Terminal branch of common iliac artery
- Begins in front of sacroiliac joint.
- Runs along the medial border of the psoas muscle
- The artery runs downward and backward and ends near the upper margin of greater sciatic foramen, where it divides into anterior and posterior divisions
- Branches:

Anterior Branches

SDMIIIV

- In Male it gives of 6 branches
  - Superior vesical (branch of umbilical artery)
  - Obturator
  - Middle rectal
  - Inferior vesical
  - Inferior gluteal
  - Internal pudendal
- The last two are terminal branches
- In Female it gives of 7 branches
  - Vaginal artery (in place of inferior vesical artery)
  - Uterine artery (is the 7th branch)

Posterior Branches

SLY

- Iliolumbar
- Lateral sacral
- Superior gluteal arteries

Superior Rectal Artery

- Continuation of inferior mesenteric artery
- Supplies rectum and upper half of anal canal

Ovarian artery

- Arises from abdominal aorta
- It crosses external iliac artery and enters the suspensory ligament of the ovary
- Then passes into broad ligament → then ovaries

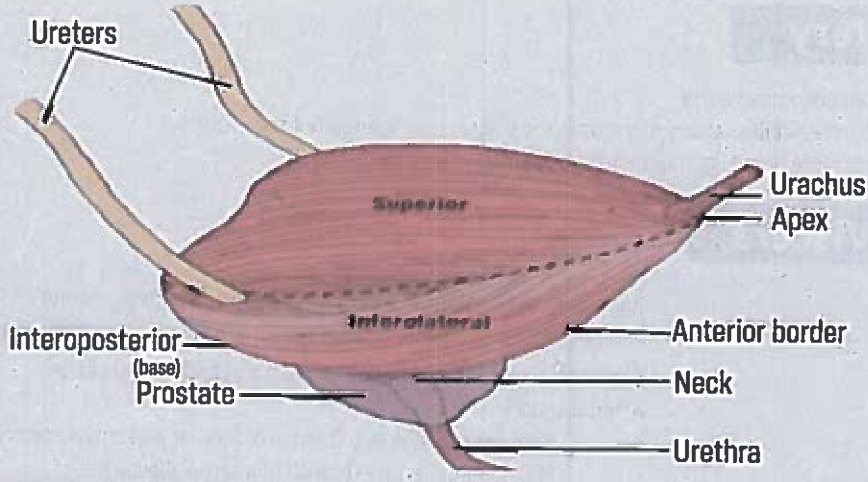
Intestinal Viscera

Sigmoid Colon	• Begins as continuation of descending colon and ends at rectum • Arterial supply → sigmoid artery (branch of inferior mesenteric artery)

Rectum	• Begins as continuation of sigmoid colon and ends at anal canal
	• Arterial supply
	  ◦ Superior rectal artery (branch of inferior mesenteric artery)
	  ◦ Middle rectal artery (branch of internal iliac artery)
	  ◦ Inferior rectal artery (branch of internal pudendal artery) T_{12} - L_3
	• Nerve supply:
	  ◦ Sympathetic and parasympathetic (via inferior hypogastric plexuses)

Ureters
A P
IUG
	• Extends from kidney to posterior surface of bladder
	• Relation of ureter
	  ◦ Anterior to iliac vessels
	  ◦ Posterior to ovarian vessels
	  ◦ This relation is important as During C-section or pelvic surgeries ureter is cut/ ligate
	• Ureter constrictions:
	  ◦ Where renal pelvis joins ureter
	  ◦ Where it crosses pelvis brim
	  ◦ Where it pierces bladder wall
	• Can be palpated via lateral fornix of vagina

Urinary Bladder (shown in fig below)	• Pyramidal in shape with capacity of 500mL has a base, apex, neck and superior surface
	  ◦ Apex → points anteriorly and is connected to umbilicus via median umbilical ligament
	  ◦ Base → made by posterior surface, triangular in shape
	  ◦ Neck → points inferiorly
	  ◦ Superior surface → covered with peritoneum
	• Ureters enters at suprolateral angles
	• Urinary bladder and prostate is separated from rectum by= Denoviller's fascia also called rectoprostatic fascia
	• The superior and part of the posterior surfaces of the bladder are covered by peritoneum
	• Inferolateral surface of the bladder is devoid of peritoneum
	• Nerve supply:
	  ◦ Sympathetic (via superior and inferior hypogastric plexus)
	  ◦ Parasympathetic (via pelvic splanchnic nerves)
	• Arterial supply:
	  ◦ Superior and inferior vesical arteries (branches of internal iliac artery)
	• Lymph drainage:
	  ◦ Internal and external iliac nodes
	• Injury to bladder (applied anatomy)
	  ◦ Injury above sacral spinal cord (above L1=UMN lesion)= spastic bladder
	  ◦ Injury below sacral spinal cord (Below L1-LMN lesion)= Atonic bladder
	  ◦ Neurogenic bladder= spastic + atonic bladder

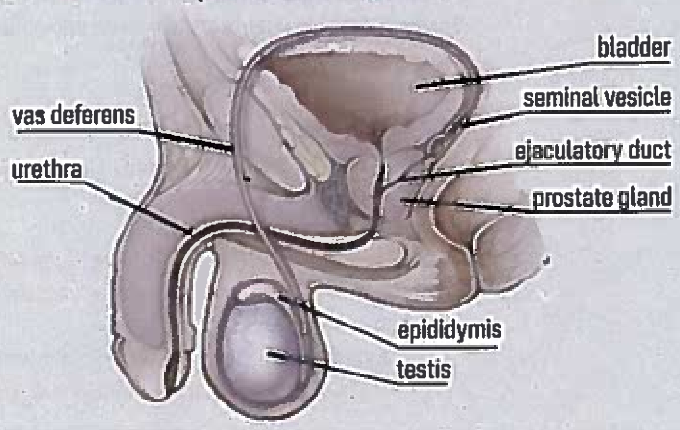


Male Genital Organs

Testes	• Paired, ovoid organs responsible for production of spermatozoa and testosterone. • Coverings of the Testis: (from outwards to inside) ◦ Tunica Vaginalis ◦ Tunica Albuginea ◦ Tunica vasculosa • Blood supply→ testicular artery (branch of abdominal aorta) • Venous drainage ◦ Right testicular vein drains into inferior vena cava ◦ Left testicular vein in to left renal vein • Applied anatomy: ◦ Because the left spermatic vein enters the left renal vein at a 90° angle, flow is less laminar on left than on right ◦ Left venous pressure > right venous pressure →varicocele more common on the left.
Vas Deferens	• Emerges from epididymis, passes through inguinal canal. • It joins the duct of seminal vesicle to become Ejaculatory duct • Conveys mature sperm from the epididymis to the ejaculatory duct and the urethra.
Ejaculatory Duct	• Two in number and formed by union of vas deferens and seminal vesicle duct • Opens into prostatic part of urethra
Seminal Vesicles	• Two in umber and lies on the posterior surface of the bladder • On the medial side of each vesicle lies the terminal part of the vas deferens. • Posteriorly, the seminal vesicles are related to the rectum • Inferiorly, each seminal vesicle narrows and joins the vas deferens of the same side to form the ejaculatory duct.
Prostate	• Lies between the neck of the bladder and surrounds the prostatic urethra • The two ejaculatory ducts pierce the upper part of the posterior surface of the prostate to open into the prostatic urethra • Prostate is separated from rectum by= Denoviller's fascia also called rectoprostatic fascia • Blood supply: ◦ Inferior vesical artery ◦ Middle rectal artery • Lymph drainage→ internal iliac nodes • Nerve supply→ inferior hypogastric plexuses

Sperm Pathway During Ejaculation (mnemonic -- SEVEN UP)

- Seminiferous tubules → Epididymis → Vas deferens → Ejaculatory ducts → (Nothing) → Urethra → Penis



Female Genital Organs

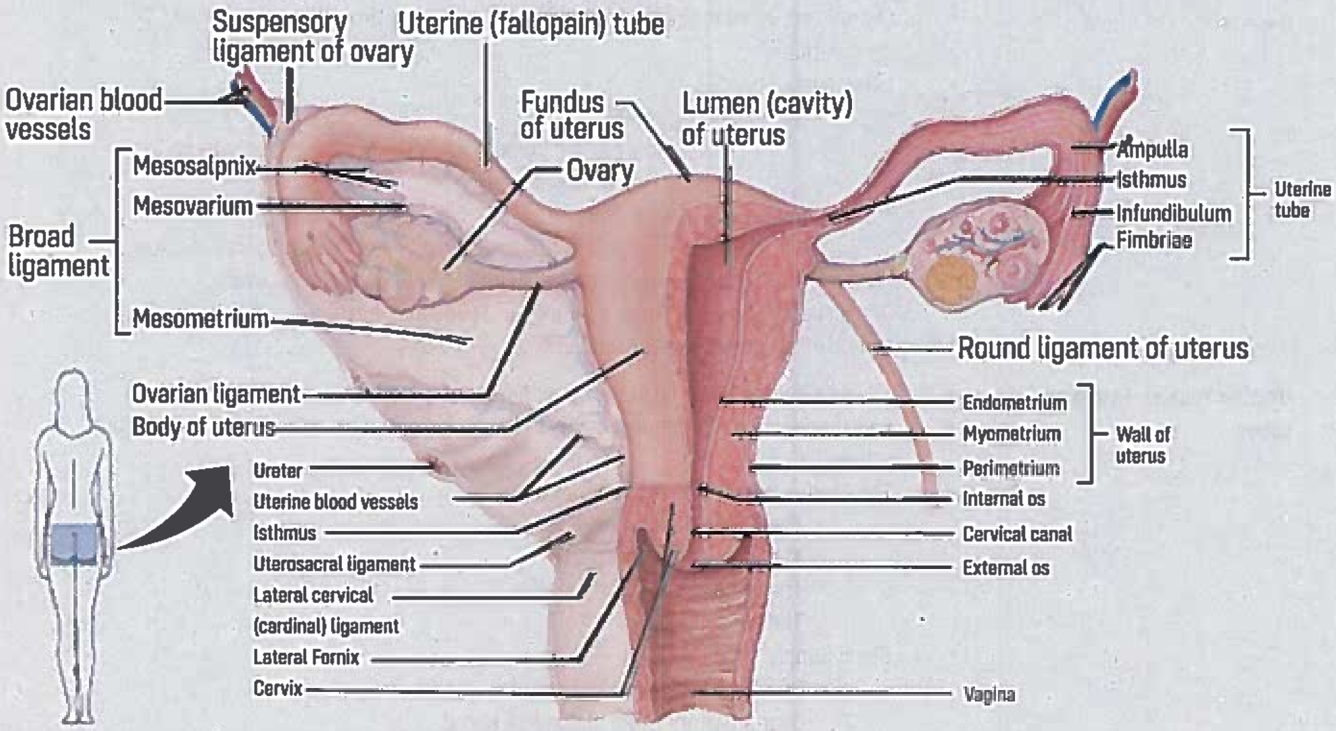
Ovaries	• Ovary is attached to the back (kept in position) of the broad ligament by the mesovarium
	• Ligaments of ovaries
	  ◦ Suspensory ligament of ovary:
	    ▪ Lateral part of the broad ligament connecting mesovarium to the lateral wall of the pelvis
	  ◦ Round ligament of ovary
	    Represents the remains of the upper part of the gubernaculum, connects the lateral margin of the uterus to the ovary
	• Blood supply → ovarian artery (branch of abdominal aorta)
	• Lymph drainage → Para-Aortic Nodes

Uterine Tube or Fallopian tubes	• The two uterine tubes lie in the upper border of the broad ligament
	• Each connects the peritoneal cavity in the region of the ovary with the cavity of the uterus.
	• The uterine tube is divided into four parts
	  ◦ The infundibulum
	  ◦ The ampulla (widest part)
	  ◦ The isthmus (narrowest part)
	  ◦ The intramural part
	• Blood Supply
	  ◦ Uterine artery (from internal iliac artery)
	  ◦ Ovarian artery (from abdominal aorta)
	• Lymph Drainage
	  ◦ The internal iliac and para-aortic nodes.
	• Nerve Supply
	  ◦ Sympathetic and parasympathetic nerves from the inferior hypogastric

Uterus	• It is divided into the fundus, body, and cervix
	• Relations:
	  ◦ Anteriorly: uterovesical pouch and the superior surface of the bladder (
	  ◦ Posteriorly: rectouterine pouch (pouch of Douglas)
	  ◦ Laterally: broad ligament and the uterine artery and vein
	• Positions of the Uterus
	  ◦ Anteversion
	    ▪ The long axis of the uterus is bent forward on the long axis of the vagina.
	  ◦ Retroverted.
	    ▪ Fundus and body of the uterus are bent backward on the vagina so that they lie in the rectouterine pouch (pouch of Douglas)

- Ligaments of uterus:
  - **Transverse Cervical (Cardinal) Ligaments** attach cervix and upper end of the vagina to lateral pelvic walls---**major support of the uterus**
  - **Pubocervical Ligaments** attach cervix to pubic bones.
  - **Sacrocervical Ligaments** attach cervix and upper end of the Vagina to the lower end of the sacrum.
  - **Broad ligaments**
    - Two layered fold of peritoneum extends from lateral margins of uterus to lateral pelvic wall
    - It provides little support to uterus
    - Contains
      - Uterine tube, round ligament of ovary and uterus, uterine and ovarian vessels
  - Round ligament of uterus
    - Extends from suprolateral angle of uterus to labia majora
    - It helps in keeping uterus anteverted and anteflexed

Female Genital Organs (continued)



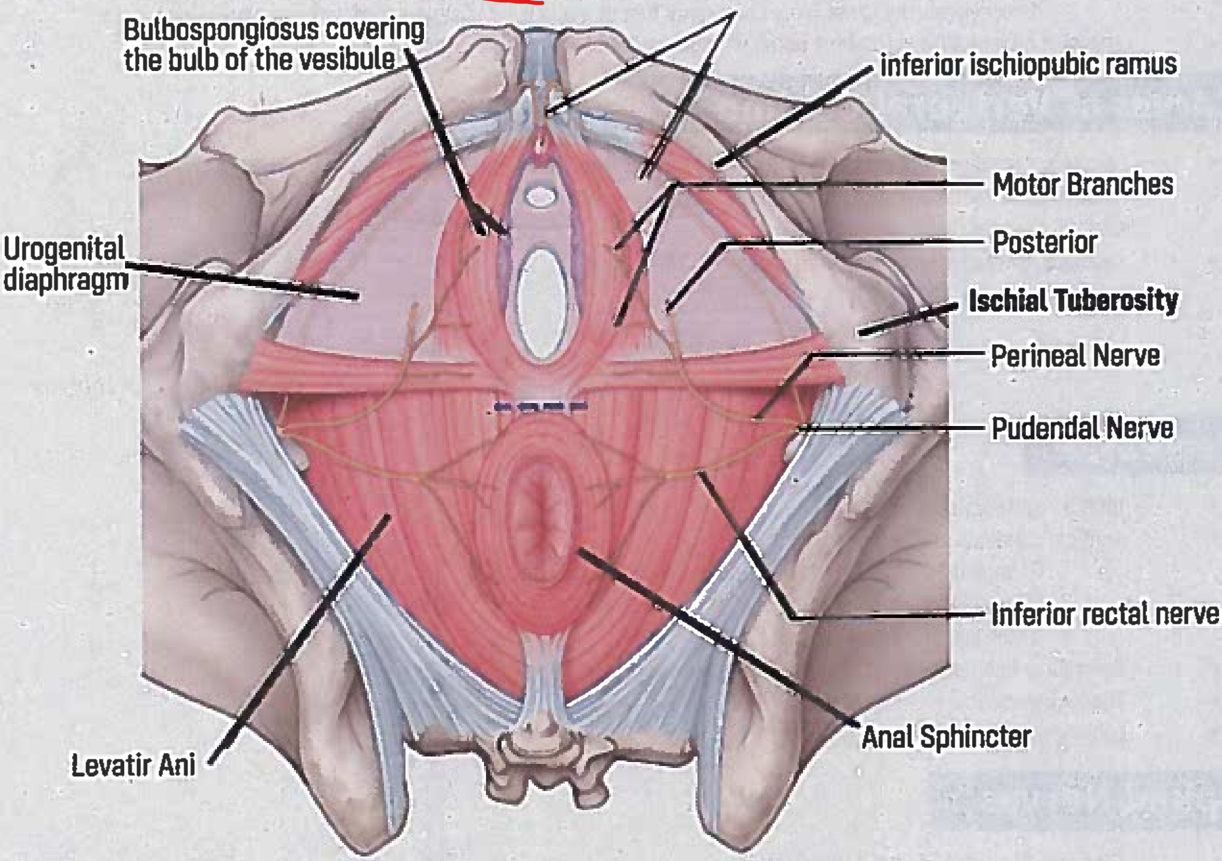
Female Genital Organs Ligaments

Ligament	Connects	Structures Contained	Notes
Suspensory ligament of the Ovary (Infundibulopelvic	Ovaries to lateral pelvic wall	Ovarian vessels	(mnemonic: water (ureter) under the bridge (ovarian artery) Ureter is related posteriorly to ovarian vessels and at risk of injury during ligation of ovarian vessels
Cardinal ligament	Cervix to side wall of pelvis	Uterine vessels	Main support of uterus
Round ligament of the uterus	Uterine fundus to labia majora		Derivative of gubernaculum.

Broad ligament	Uterus, fallopian tubes, and ovaries to pelvic side wall	Ovaries, fallopian tubes, round ligaments of uterus	
Ovarian ligament	Medial pole of ovary to lateral uterus		Derivative of gubernaculum.

Ischiorectal Fossa Boundaries

- Superiorly: levator ani
- Medially:
  - Levator ani
  - External anal sphincter
- Laterally:
  - Ischial tuberosity and obturator muscle
- Contents:
  - Pudendal nerve and vessels
  - Inferior rectal vessels and inferior anal nerve



Urogenital Triangle

- Layer of the pelvis that separates the deep Perineal sac from the upper pelvis
- It lies between the inferior fascia of the urogenital diaphragm (Perineal membrane) and superior fascia of the urogenital diaphragm.
- Laterally attached to= ischiopubic rami

Chapter 6:
Back and Vertebral Column

Vertebral Column

- The vertebral column is composed of 33 vertebrae
  - 7 cervical
  - 12 thoracic
  - 5 lumbar
  - 5 sacral (fused to form the sacrum)
  - 4 coccygeal (the lower 3 are commonly fused). Because it is segmented and made up of vertebrae,
- The intervertebral discs (pads of fibrocartilage) form about 1/4th the length of the column

Curves of Vertebral Column

- Lordosis: the spine curves significantly inward at the lower back.
- Kyphosis. Characterized by an abnormally rounded upper back (more than 50 degrees of curvature).
- Scoliosis. Characterized by sideways curve to their spine.

Scoliosis Kyphosis Lordosis

Vertebrae

- Total 33 vertebrae.
- Atypical cervical vertebrae:
  - C1 vertebrae (atlas) → no body, no spine articulate above with occipital and below with axis.
  - C2 vertebrae (axis) → peglike odontoid process
  - C7 vertebrae → longest spine
- Transverse ligament → supports odontoid process of axis on atlas
- Thoracic vertebrae → heart shaped
- Lumbar vertebrae → kidney shaped

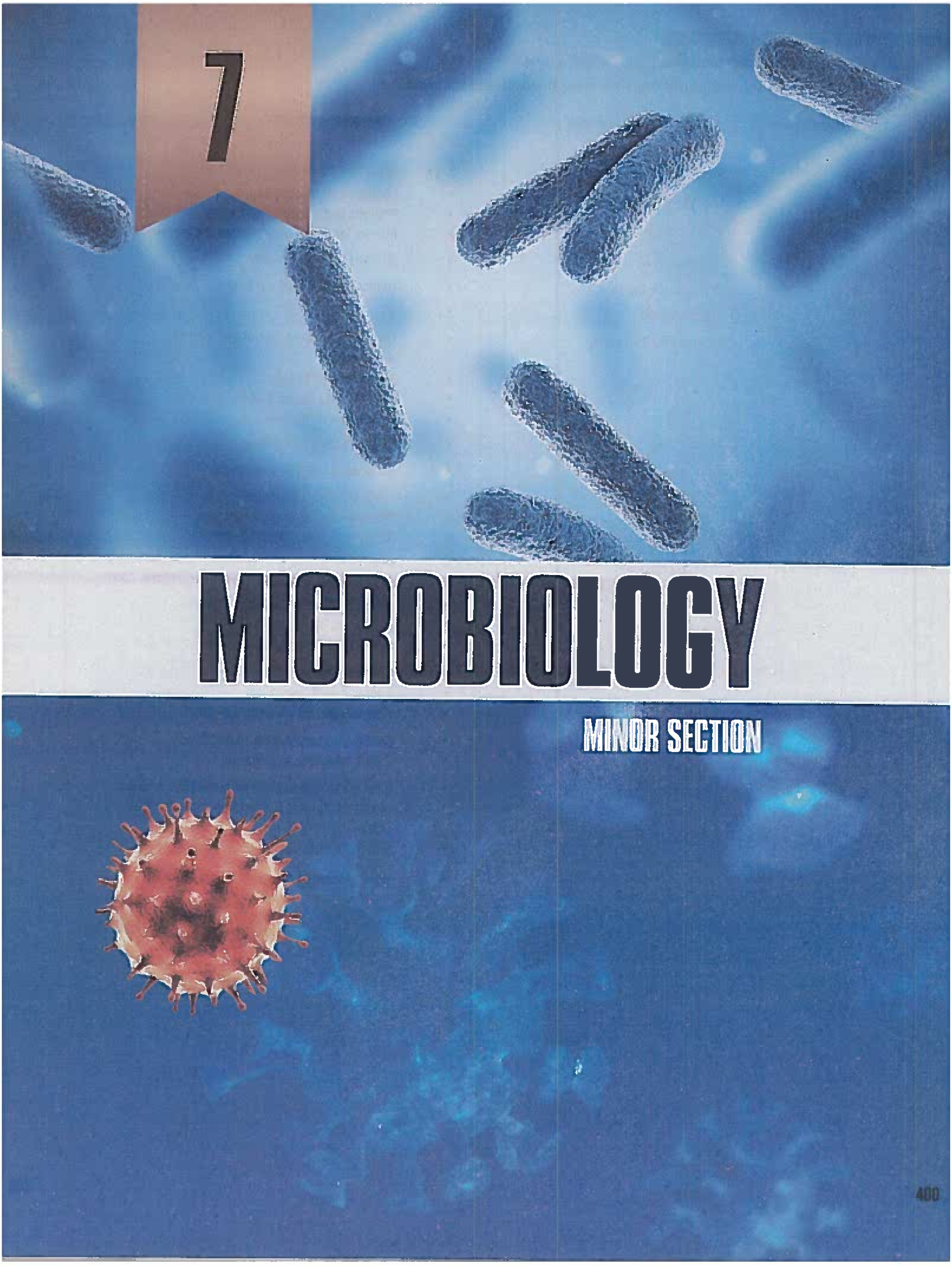
Spinal Nerves

- There are 31 pairs of spinal nerves in total
- 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.
- Nerves C1-C7 exit above the corresponding vertebra.
- C8 spinal nerve exits below C7 and above T1.
- All other nerves exit below the corresponding vertebrae (e.g., C3 exits above the 3rd cervical vertebra; L2 exits below the 2nd lumbar vertebra)

Vertebral Levels

- Landmarks and internal structures found at various vertebral levels.

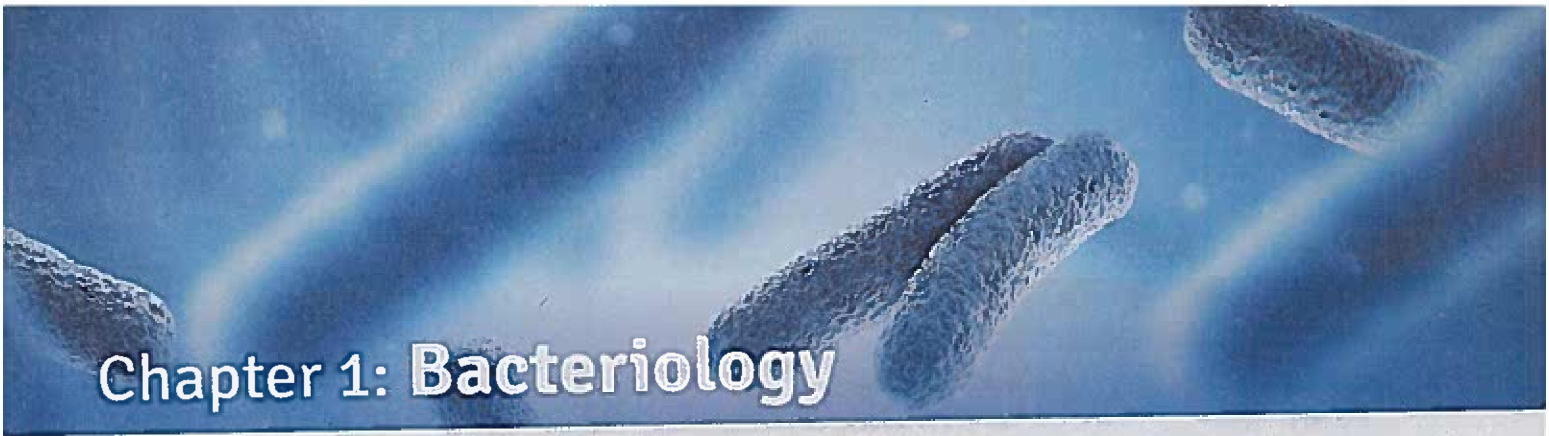
Vertebral Level	Landmark	Internal Significance
C3	Hyoid bone	
C4	Superior border of thyroid cartilage	• Bifurcation of common carotid artery
C6	Cricoid cartilage	• Larynx ends; trachea begins • Pharynx ends; esophagus begins • Inferior laryngeal nerve enters the larynx.
C7	Vertebra prominence	• Isthmus of thyroid gland
T1	Sternoclavicular joint	• Highest point of apex of lung.
T2	Jugular notch	•
T4	Sternal angle (of Louis)	• Division between superior and inferior mediastinum • Ascending aorta ends • Arch of aorta begins & ends. • Bifurcation of Trachea
T8		• Inferior vena cava passes through diaphragm
T10		• Esophagus through diaphragm
T12		• Aorta through diaphragm • Thoracic duct through diaphragm • Azygous V. through diaphragm
L1	Tran pyloric plane	• Pylorus of stomach. • Duodenojejunal flexure • Origin of Superior Mesenteric artery • Coccygeal ligament starts • Spinal cord termination in adults
L2		• Cisterna chyli ends • Thoracic duct begins • Azygous and Hemiazygous begin
L3		• Spinal cord termination in childrens • Conus medularis in childrens
L4/L5	Iliac crest	• Bifurcation of aorta into common iliac arteries • Inferior vena cava formed from common iliac veins • Site for lumbar puncture
S2		• Dura, arachnoid, Subarachnoid space ends



7

MICROBIOLOGY

MINOR SECTION



Chapter 1: Bacteriology

Classification

Morphology	Gram positive	Gram negative
	Mnemonic: Strong Corny Actors KNock Back Listerine in the Closet - the gram positive bacteria are Staph, and Strep (the t looks like a + sign) • Corynebacteria, • Actinomyces • Nocardia, • Bacillus • Listeria • Clostridium.	
Coccus (Spherical In Shape)	• Staphylococcus (clusters) • Streptococcus (chains or pairs)	• Moraxella catarrhalis • Neisseria
Bacilli (Rod In Shape)	*All bacilli are gram negative except* **"L.DATTA"** • Listeria (**causes ataxia,** pneumonia, seizures---diagnosis by Blood culture, CSF reveals **tumbling motility**) • Diphtheria • Actinomyces • Tetani Clostridium • *TB Mycobacterium (acid fast)* • *Anthrax bacillus (**painless** black skin lesions—**treatment ciprofloxacin**)*	**Enterics:** (Mnemonic: Eating High Contaminated Stuff Produces Big Smelly Vomit) • E. coli • Helicobacter pylori • Campylobacter (complications include GBS) • Salmonella • Pseudomonas • Bacteroides • Shigella • Vibrio **Respiratory:** (Habib Bank Limited) • Haemophilus (pleomorphic) • Bordetella • Legionella (**silver stain**)

Spiral		Spirochetes: (BoLT)
		• Borrelia (LYME disease—Rx Doxycycline (1st choice/ amoxicillin)
		• Leptospira
		  ◦ Causes leptospirosis (aka Weil's disease)
		  ◦ **Main clue in questions are occupation,**
		  ◦ Common in sewage workers, farmers, vets
		  ◦ Spread by rat urine
		  ◦ Causes hepato-renal failure and sub
		  ◦ conjunctival hemorrhage,
		• Treatment –**benzylpenicilin or doxycycline**

No Cell Wall		• Mycoplasma **(contains sterols which do not gram stain)** • Chlamydiae • Rickettsiae

Comparison of Gram ⊕ and Gram ⊖ Organism

Features similar in both	• Cell wall→outer covering • Cell membrane→phospholipid bilayer, site of oxidative enzymes • *Capsule→polysaccharide layer, protect against phagocytosis* • *Flagellum→helps in motility* • *Pilus→helps in adherence of bacteria to cell surface*
Features specific to gram ⊕	• Produces exotoxins only. • Lipoteichoic acid→induce TNF-α and IL-1. • *Spores→highly resistant to heat, not killed by 100°, but killed at 121° for 15 minutes (autoclaving)*

Features specific to gram ⊖	• Produces exotoxins as well as endotoxins
	• Lipopolysaccharide also called endotoxins
	• *Virulence is associated with toxin production*
	• **ENDOTOXINS** results in:
	  ◦ **E**dema
	  ◦ *Nitric oxide (causing vasodilation resulting in hypotension)*
	  ◦ **D**IC/Death
	  ◦ **O**uter membrane
	  ◦ **T**NF-α
	  ◦ *O-antigen + core polysaccharide + lipid A (components of endotoxins)*
	  ◦ e**X**tremely heat stable
	  ◦ *IL-1 and IL-6 (resulting in fever)*
	  ◦ **N**eutrophil chemotaxis
	  ◦ **S**hock

Encapsulated Bacteria

- **Mnemonic:** **P**lease **SHINE** my **SKiS**
  - **P**seudomonas aeruginosa,
  - **S**treptococcus pneumoniae A
  - **H**aemophilus
  - **I**nfluenzae type B,
  - **N**eisseria meningitidis,
  - **E**scherichia coli,
  - **S**almonella
  - **K**lebsiella pneumoniae
  - group B **S**trep

Encapsulated Bacteria And Vaccines

- Encapsulated bacteria are opsonized, and then cleared by spleen.
- Asplenics have↓opsonizing ability and thus ↑risk for severe infections.
- Therefore give the following vaccines
  - *Pneumococcal vaccine*
  - *H influenzae vaccine*
  - *Meningococcal vaccine*

Pigment Producing Bacteria

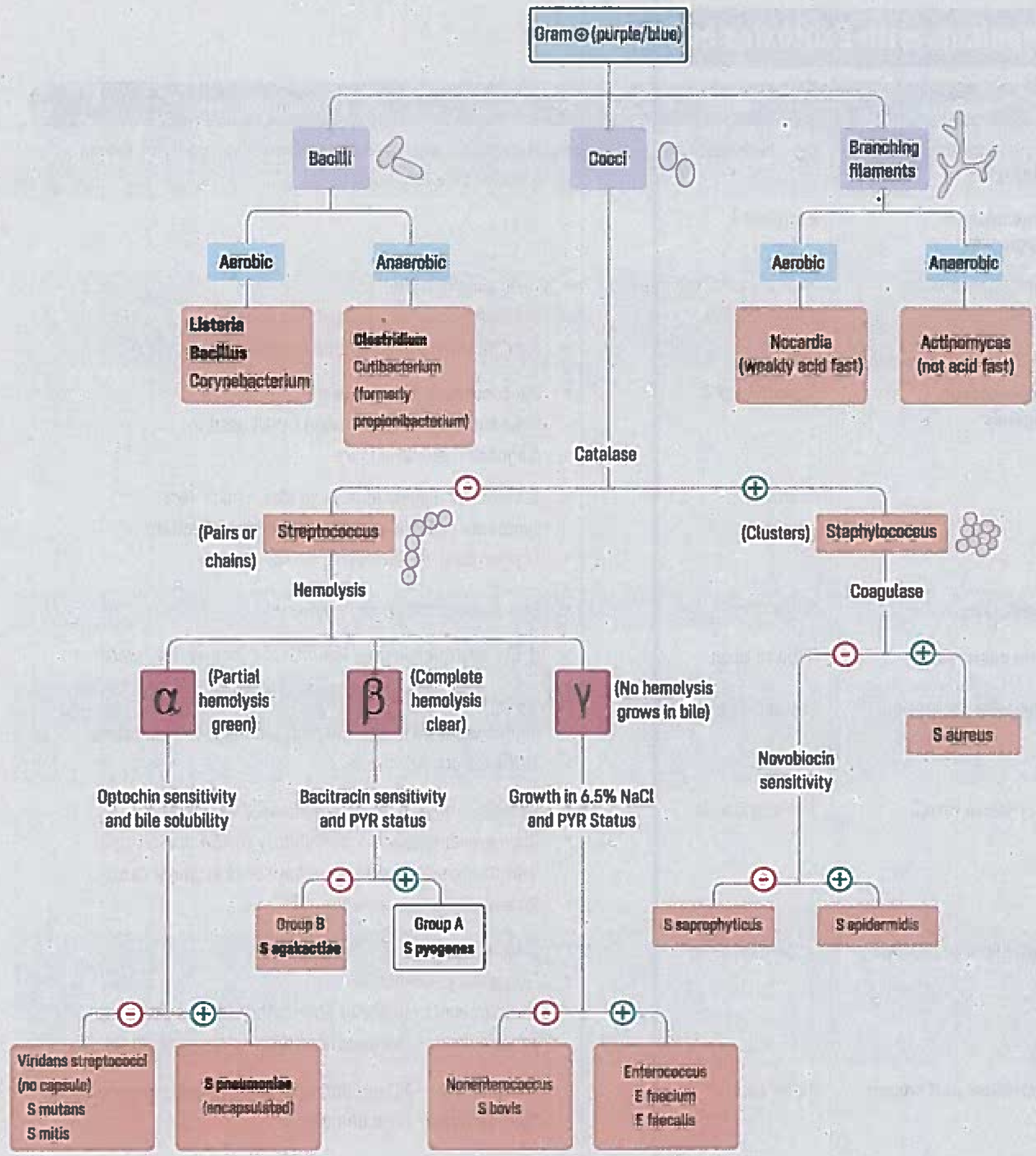
Organisms	Pigment	Mnemonic	Notes
• Actinomyces **Israelii**	• **Yellow** "sulfur" granules	• **Israel** has **yellow** sand	• *Causes granuloma and abscess*

• S. aureus	• Yellow pigment	• Aureus (Latin) = gold (yellow)	
• P. aeruginosa	• blue-Green pigment	• Aerugula is green	

Organisms with Exotoxins and Diseases

Bacteria	Toxin	Manifestation
Corynebacterium diphtheriae	Diphtheria toxin	• Pharyngitis with *pseudomembranes in throat and severe lymphadenopathy (bull neck)*
Pseudomonas aeruginosa	*Exotoxin-A*	
Staphylococcus aureus	*Toxic shock syndrome toxin (TSST-1)*	• Toxic shock syndrome: • *Scalded skin syndrome (exfoliative toxin)* • *Food poisoning (heat-stable enterotoxin)*
Streptococcus pyogenes	Streptolysin-O	• Contributes to β-hemolysis. • Host antibodies against toxin (ASO) used to diagnose rheumatic fever
	Exotoxin A	• Toxic shock-like syndrome: (a toxic shock-like syndrome associated with painful skin infection). • *Scarlet fever (erythrogenic toxin)*
Shigella spp.	*Shiga toxin*	• GI mucosal damage→dysentery
Vibrio cholerae	Cholera toxin	• *↑Cl- secretion in gut, Voluminous "rice-water" diarrhea*
Bordetella pertussis	Pertussis toxin	*Whooping cough* • Child coughs on expiration and "whoops" on inspiration • *"100-day cough" in adults*
Clostridium tetani	*Tetanospasmin*	• *Spastic paralysis, risus sardonicus, and "lockjaw".* • *Toxin prevents release of inhibitory (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord* • *Spread via motor neurons*
Clostridium botulinum	Botulinum toxin	• *Flaccid paralysis,* • *Floppy baby syndrome* • *Toxin prevents release of stimulatory (ACh) signals at neuromuscular junctions resulting in flaccid paralysis*
Clostridium perfringens	*Alpha toxin*	• Phospholipase→Degradation of phospholipids *myonecrosis ("gas gangrene")* and hemolysis.

Gram ⊕ Classification



Important **tests** are in **bold**. Important ***pathogens*** are in ***bold italics.***

Note: Enterococcus in either α or β hemolytic.

Gram Positive Organisms

1. Gram ⊕ Cocci

Catalase	*Catalase ⊕ organism*	*Staphylococcus*
	Catalase ⊖organism	*Streptococcus*

Staphylococcus	Coagulase ⊕	S. aureus	• *Toxic shock syndrome (TSST-1) (Diagnostic Criteria)* ◦ Associated with vaginal colonization and tampon use in women ◦ High grade fever, hypotension, diffuse erythematous rash ◦ **Desquamation of rash**, especially of the palms and soles ◦ Involvement of 3 or more organs ◦ Treatment: Flucloxacillin **or** vancomycin **plus** clindamycin • *Scalded skin syndrome (exfoliative toxin).* ◦ ffects children <5 years ◦ Fluid filled blisters ◦ Treatment: Flucloxacillin • *Food poisoning (enterotoxins)* • *Organ abscesses, pneumonia, endocarditis,* • Septic arthritis, and *osteomyelitis*
	Coagulase ⊖	S. epidermidis	• *Normal flora of skin* • *Contaminates blood cultures.* • *Infects prosthetic devices (e.g., hip implant, heart valve)* • *Infect IV catheters*
		S. saprophyticus	• **Normal flora of female genital tract and perineum.** *Second most common cause of uncomplicated UTI in young women (most common is E coli).*
Streptococcus	**α- hemolysis** i.e. partial hemolysis	Optochin sensitivity⊕ →S. pneumonia	Most common cause of: • Meningitis • Otitis media (in children) • *Bacterial pneumonia* • *Sepsis in Asplenic patients*
		Optochin sensitivity⊖ →S. viridans	• *Most common cause of IE* • Dental caries • *Subacute bacterial endocarditis at damaged heart valves*
	β- hemolysis i.e. complete hemolysis	Bacitracin sensitivity ⊕ →Group A S. pyogenes	• *Scarlet fever* ***(erythrogenic toxin)*** • *Toxic shock-like syndrome* • *Rheumatic fever* • *Post-Streptococcal glomerulonephritis* • Pharyngitis and *cellulitis (major organism).*
		Bacitracin sensitivity ⊖ Group B →S. agalactiae	(Group B = Babies) • Pneumonia, *meningitis (main cause of meningitis in new born),* and sepsis, mainly in Babies

	γ -hemolysis i.e. no hemolysis	Growth in 6.5 % NaCl ⊕→ Group D (enterococcus)	
		Growth in 6.5 % NaCl ⊖→ Nonent erococcus S. bovis	(Bovis in the Blood = Cancer in the Colon) • *Subacute endocarditis* • *Associated with colon cancer.*

2. Gram ⊕ Bacilli

Clostridium (Spore forming rods)	**Clostridium tetani**	• *Spastic paralysis, risus sardonicus, and lockjaw (trismus).*
		• *Toxin prevents release of inhibitory (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord*
		• *Spread via motor neurons*
		• Treatment ----
		  • Supportive— ventilaroty support , relaxants
		  • **Metronidazole now preferred to benzylpenicilin as the drug of choice**

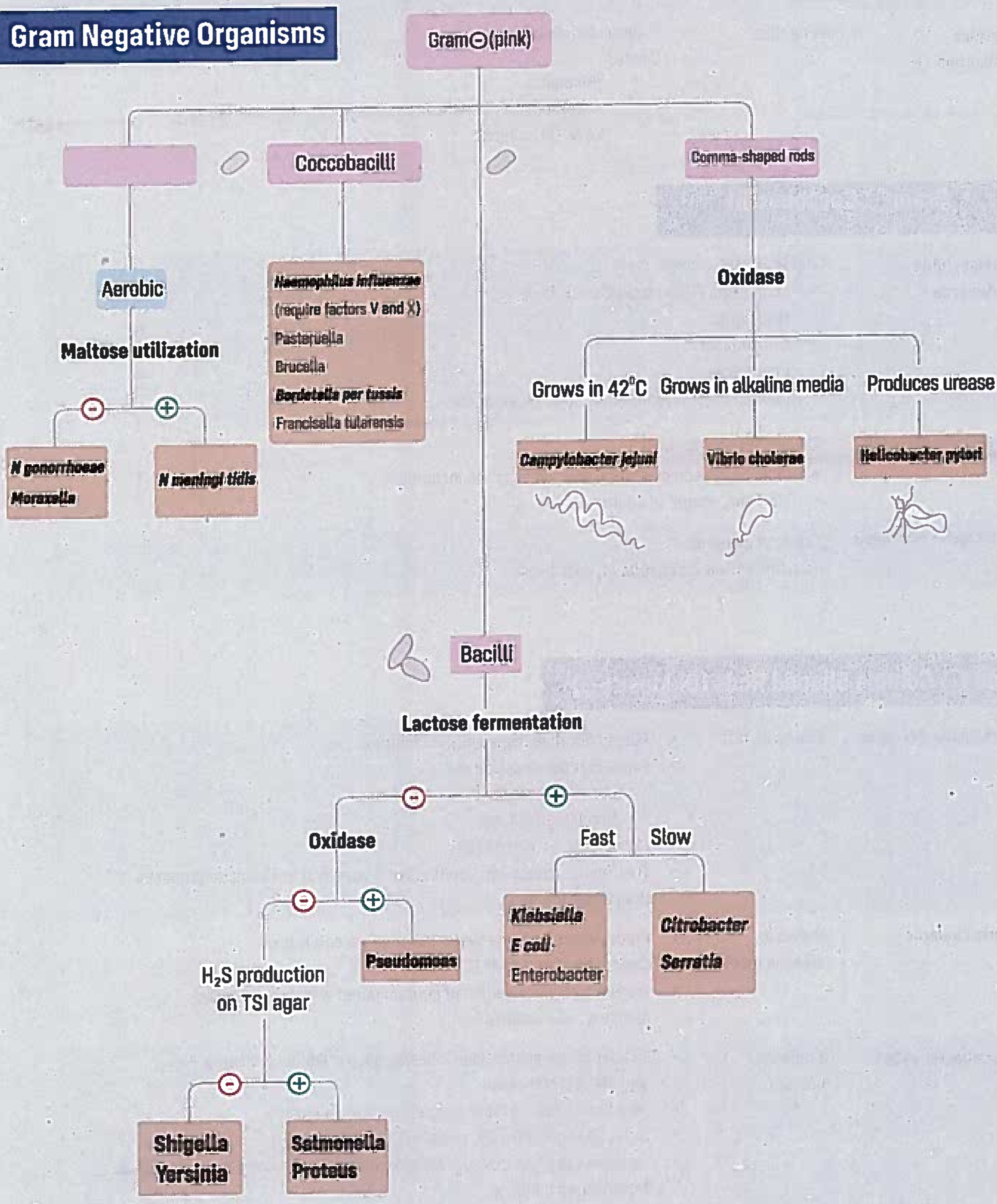
	Clostridium botulinum	• *Flaccid paralysis,* • *floppy baby syndrome* • *Toxin prevents release of stimulatory (ACh) signals at neuromuscular junctions resulting in flaccid paralysis*
	Clostridium perfringens	• Phospholipase→Degradation of phospholipids→myonecrosis ("gas gangrene") and hemolysis.

	Clostridium difficile	• *Pseudomembranous Colitis often 2° to antibiotic use*
		• *Treatment:*
		  • *Metronidazole (10-14 days), if no response then oral vancomycin*
		  • ***For life threating complications metronidazole + vancomycin***

My cobacterium	**Mycobacterium tuberculosis**	Attaches to cell surface Causes Tuberculosis • *Symptoms include night sweats, weight loss, cough* • *Caseating granulomas with central necrosis and Langhans giant cells are characteristic of 2° tuberculosis*
	M. avium	• *Disseminated non-TB disease in AIDS*
	Mycobacterium leprae	*Attaches to intracellular* *Causes leprosy:* • *Non-caseating granuloma* • *Causes nasal bridge deformity* • *Acid Fast Bacilli* • *Damages nerve →↓Reflexes* • *Glove and stocking sensory loss* Treatment: Dapsone and rifampin
Corynebacterium diphtheria		Causes diphtheria Symptoms include:

	• Pseudomembranous • Pharyngitis (grayish-white membrane) • With lymphadenopathy, myocarditis
Bacillus cereus	*Reheated rice syndrome.* • Spores survive cooking rice. Keeping rice warm results in germination of spores and enterotoxin formation

Gram Negative Organisms



- **Gram ⊖ Cocci**

Maltose utilization ⊖	N. gonorrhoeae	• No polysaccharide capsule • Causes ◦ Gonorrhea, septic arthritis ◦ Neonatal conjunctivitis (2-5 days after birth) ◦ Pelvic inflammatory disease (PID) ◦ Fitz-Hugh-Curtis syndrome
	Moraxella	
Maltose utilization ⊕	N. meningitidis	• Polysaccharide capsule • Causes ◦ Meningitis. Waterhouse-Friderichsen syndrome (adrenal insufficiency, fever, DIC, shock)

• Gram⊖ Coccobacilli

Haemophilus influenzae	HaEMOPhilus causes • Epiglottitis ("thumb sign" on x-ray), • Meningitis, • Otitis media • Pneumonia Treatment is ceftriaxone/ amoxicillin-clavulanate.
Bordetella pertussis	Causes Whooping cough • Child coughs on expiration and "whoops" on inspiration • "100-day cough" in adults
Francisella tularensis	Causes Tularemia *Transmitted via Ticks, rabbits, deer flies*

Gram ⊖ Comma Shaped Rods (Oxidase ⊕)

Campylobacter jejuni	Grows in 42°C	• Bloody diarrhea (especially in children). • Fecal-oral transmission via ◦ *Contaminated poultry or meat* ◦ *Unpasteurized milk.* • *Complications include GBS* • Treatment: usually self-limiting but if severe or immunocompromised then Clarithromycin
Vibrio cholerae	Grows in alkaline media	• *Produces profuse rice-water diarrhea via enterotoxin* • *Cannot be stored at 4° C,* • Transmitted via ingestion of contaminated water or uncooked food (e.g., raw shellfish).
Helicobacter pylori	Produces urease	• Risk factor for peptic Ulcer disease, gastric adenocarcinoma, and MALT lymphoma. • Urea breath test or fecal antigen test for diagnosis • Triple ⊕→catalase ⊕, oxidase⊕, and urease ⊕ • Treatment is triple therapy→Amoxicillin + Clarithromycin + Proton pump inhibitor.

• Gram ⊖ Bacilli

Lactose fermentation ⊕	**Klebsiella**	Intestinal flora 5 A's of KlebsiellA: • *Aspiration pneumonia (in Alcoholics and DiAbetics)* • *Abscess in lungs and liver* • *"Curr-A-nt jelly" sputum (blood/mucus)*
	E. coli	Four strains • EIEC→Invasive; dysentery • *ETEC→Travelers' diarrhea* • EPEC→Diarrhea (Pediatrics) • *EHEC→Hemolytic-uremic syndrome (which is triad of anemia, thrombocytopenia, and acute renal failure)*
Lactose fermentation ⊖	**Pseudomonas aeruginosa**	Oxidase ⊕. Toxin→Exotoxin A Causes: (PNS) • Pneumonia • Nosocomial infections (catheters, equipment) • Sepsis
	Salmonella	Oxidase ⊖, and can invade the GI tract via M-cells of Peyer patches. Causes • Other salmonella spp.→Diarrhea Salmonella typhi→Typhoid (Diagnosis BASU→ 1st week Blood culture, 2nd week→Agglutination (Widal test/typhidot), 3rd week→Stool culture, 4th week Urine culture)
	Shigella	Oxidase ⊖, and can invade the GI tract via M-cells of Peyer patches. Causes: • Bloody diarrhea (bacillary dysentery)

Other Important Bacteria's and Important Infectious Diseases

Chlamydia vs. Gonorrhea

	Chlamydia	Gonorrhea
Caused by	• *Chlamydia trachomatis, STD*	• *Neisseria gonorrhea, STD*
Serotypes	• *Serotypes A, B and C= Trachoma (follicular conjunctivitis with corneal scarring)* • *Serotypes L1- L3= Lymphogranuloma* • *enerum* • *Serotypes D-K – STD*	

Complications	• *Reiter's syndrome = Urethritis, conjunctivitis, arthritis*
	• Fitz- Hugh-Curtis syndrome= Peri-hepatic inflammation and fibrosis
	• Infertility and ectopic pregnancy
		• Local complications that may develop include urethral strictures, epididymitis and *salpingitis (hence may lead to infertility).*
		• Disseminated Gonococcemia
		  · Septic arthritis
		  · Rash
		  · Tenosynovitis

Treatment	• Azithromycin 1g (single dose)---first line treatment Or • Doxycycline (7 days) If pregnant = erythromycin or amoxicillin	• Ceftriaxone 500 mg intramuscularly as a single dose with azithromycin 1 g oral as a single dose.
Investigations	• *NAATs (nuclear acid amplification test) = investigation of choice*	• *Gram stain and culture= investigation of choice* • NAATs (nuclear acid amplification test)
	Lymphogranuloma venereum (LGV) • Infection comprises of three stages ◦ Stage 1: small painless pustule which later forms an ulcer ◦ Stage 2: **painful inguinal** lymphadenopathy ◦ Stage: 3 Proctitis • Treatment= Doxycycline	
Guidelines	• Men (symptomatic)= all partners within **four weeks** should be contacted • Women and asymptomatic men= all partners from **last 6 months** should be contacted • Contacts positive = offer treatment prior to investigation **(treat then test)**	• Gonorrhea and Chlaymdia co-infections are eXtremely common
Hint	• *Nonspecific urethritis= chlamydia*	• *Specific urethritis= gram negative diplococci= Gonorrhea*

Syphilis

Caused by	*Treponema palladium*
	Primary syphilis • Localized disease presenting with **painless chancre** **Secondary syphilis** • Disseminated disease, *maculopapular rash*, condylomata lata (painless, wart-like white lesions on genitals), and lymphadenopathy. • ***Snail track ulcers*** *in buccal mucosa* **Tertiary syphilis:** • Chronic granulomas (gummas). ***Neurosyphilis (tabes dorsalis, Argyll Robertson pupil-*** *constricts with accommodation but is not reactive to light;* also called "prostitute's pupil" since it accommodates but does not react). • Signs: **broad-based ataxia, ⊕ Romberg, Charcot joint, stroke without hypertension.** **Features of congenital syphilis** • Blunted upper incisors teeth (Hutchinson's teeth) Linear scars at angle of mouth (rhagadea) Saddle nose, deafness
Diagnosis	• *Specimen obtained from genital sores* • Diagnosis:

	• *Serologic testing--- VDRL (nonspecific)* • Becomes negative after treatment • Also raised in pregnancy, SLE, TB, leprosy, malaria and HIV • *Confirmatory diagnosis--- **FTA-ABS*** • For Neurosyphilis: test spinal fluid with VDRL, FTA-ABS, and PCR
Treatment	• *Benzyl penicillin* • *Alternatives: doxycycline* • **The Jarisch-Herxheimer reaction** is sometimes seen following treatment. Fever, rash, tachycardia after first dose of antibiotic. It is thought to be due to the release of endotoxins following bacterial death and typically occurs within a few hours of treatment (Also seen in Lyme disease)

Typhoid and Paratyphoid Fever (aka Enteric fever)

- **Introduction:**
- Agent:
  - Typhoid: Salmonella typhi
  - Paratyphoid: Salmonella Paratyphi A, B & C

Clinical features

1st week	• High grade fever –**continuous (step ladder like pattern)** • Headache, anorexia, abdominal pain • **Constipation** (due to payers patches narrowing lumen) • Relative bradycardia
2nd week	• **Rose-Spots** (rash on upper abdomen and lower chest which blanch on pressure). • Splenomegaly. • Distention of abdomen. • **Diarrhea**

3rd week	• Laying still, delirious
	• Life threating complications
	  • **GI bleed and perforation**—most common and dangerous complication
	  • Others include ---Myocarditis, pneumonia, pancreatitis

4th week	• Recovery period begins if patient survives

- **Diagnosis (Mnemonic : BASU)—remember culture is the gold standard**
  - *1st week Blood culture,*
  - 2nd week Agglutination (Widal test/ typhidot),
  - Widal test
    - O antibody > 1:160 suggestive and diagnostic
    - H antibody signifies previous infection
  - Typhidot:
    - IgM – recent infection
    - IgG – remote infection
  - 3rd week Stool culture,
  - 4th week Urine culture

- **Management**
  - Supportive
    - Proper hydration and nutrition.
    - Blood transfusion if needed.

If intestinal perforation- surgery

- Specific (any one of the following)
  - Ceftriaxone.
  - Cefixime
  - Fluoroquinolones such as ofloxacin
- Prevention
  - Hand washing.
  - Improved hygiene & clean water.
  - Eggs should be thoroughly cooked and never eaten raw.
  - Passive immunization.
  - TAB vaccine 0.25 ml subcutaneously.
  - Oral vaccine (vivotef)---------Four capsules on alternate day in children older than 6 years.

Chapter 2: Virology

DNA Viruses

- All replicate in the nucleus (except Poxvirus). "Pox is out of the Box (nucleus)."
- All are double stranded except Parvo virus (which is single stranded)

VIRUS Family (HHAPPPPy)	Example	Importance/ disease
Herpes Viruses	Herpes simplex virus-1	• *Herpes labialis*, Keratoconjunctivitis
	Herpes simplex virus-2	• *Herpes genitalis*
	Varicella-Zoster virus (HHV-3)	• Varicella-zoster(chickenpox, shingles)
	Epstein-Barr virus (HHV-4)	• *Mononucleosis (⊕ Monospot test→heterophile Antibodies)* ◦ *Fever, hepatosplenomegaly, lymphadenopathy* ◦ *Associated with lymphomas (e.g., Burkitt lymphoma)* ◦ ***Type of cell affected = B-cells*** ◦ ***Atypical cells that proliferate in response= T-cells)*** ◦ *Hint----URTI + taken amoxicillin/ampicilin develops rash---diagnosis is of IM* ◦ Avoid playing contact sports to avoid risk of splenic rupture
	Cytomegalovirus (HHV-5)	• *Mononucleosis (⊖Monospot) in immunocompetent patients* ◦ *Infection in immunocompromised, especially pneumonia* ◦ *In transplant patients, AIDS retinitis* ◦ *Infected cells have characteristic "owl eye" inclusions*
	HHV- 6 and 7	• Roseola infantum
	HHV-8	• *Kaposi sarcoma (neoplasm of endothelial cells). Seen in HIV/AIDS and transplant patients*
Hepadna virus	HBV	• The only hepatitis virus which is DNA virus.
Adenovirus		
Poxvirus		
Parvovirus	B19 virus	• *Aplastic crises in sickle cell disease,* • *"Slapped cheek" rash in children (erythema infectiosum, or fifth disease*
Papillomavirus	HPV-	• ***Warts** (caused by HPV 6-11) and **cervical cancer** (HPV 16 & 18)* • Warts management: ◦ Topical podophyllum or cryotherapy---first line ◦ Topical imiquimod---second line
Polyomavirus		

RNA Viruses

- All replicate in the cytoplasm (except influenza virus and retroviruses).

Rotavirus		The most important global cause of infantile gastroenteritis
Yellow fever virus		A flavivirus (also an arbovirus) transmitted by Aedes mosquitoes. Virus has a monkey or human reservoir

Rubella virus		A togavirus causing Rubella
		• *Also known as German (or 3-day) measles.*
		• Fever, lymphadenopathy, rash that starts on face and spreads to trunk and extremities
		• *Congenital rubella findings include*
		  · *"blueberry muffin" appearance* due to dermal extramedullary hematopoiesis
		  · *Sensorineural deafness, congenital cataracts, PDA*

Paramyxovirus	Parainfluenza virus	Group (acute laryngotracheobronchitis) • *Barking cough and inspiratory stridor.* • *Steeple sign on x-ray* • *Pulsus paradoxus 2° to upper airway obstruction*
	Measles virus	Fever with cough, coryza, and conjunctivitis *Koplik spots* followed 1–2 days later by a maculopapular Rash that starts at the head/neck and spreads downward. Complications include: • *SSPE (subacute sclerosing panencephalitis),encephalitis* • *Bacterial pneumonia, otitis media*
	Mumps virus	Includes Parotitis Complications include: *Orchitis and pancreatitis.*
Rabies virus	• Bullet-shaped virus *Negri bodies (cytoplasmic inclusions) seen.* Progression of disease: · Fever→agitation, photophobia, hydrophobia,→Hypersalivation→paralysis, coma→death. • Infection spreads from bat and dog bites.	
Ebola virus	• Targets endothelial cells, hepatocytes. High mortality rate. • Symptoms include • Flu-like symptoms, fever, diarrhea/vomiting, and myalgia. • Diagnosis→RT-PCR. • Transmission requires direct contact with bodily fluids, infected bats or primates (apes/monkeys • Supportive care, no definitive treatment.	
Zika virus	• Transmitted by Aedes mosquito bites. • Causes conjunctivitis, low-grade pyrexia, and itchy rash in 20% • cases • Diagnose→RT-PCR • Supportive care, no definitive treatment	
HIV virus		
Hepatitis viruses	• *All hepatitis viruses are RNA, except HBV*	

Some Other Important Viruses and Important Infectious Diseases

Hepatitis Virus

Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
• HAV-RNA VIRUS • Orofecal route • NO chronic state • no HCC	• *HBV-DNA virus* • carrier stage • HCC	• HCV-RNA virus • carrier stage • HCC	• HDV-RNA • Highest fatality rate • association with HBV • Incidence ↑ in IV drug users	• RNA virus • Orofecal route • Fulminant hepatitis in pregnant women

- Note: after immunization with hep-B vaccine
  - Anti-HBs
    - Normal value is >100 mIU/mL----should still receive a booster dose at 5 years
    - 10-100 mIU/mL---suboptimal response, one additional vaccine dose should be given
    - <10 mIU/mL----Non responder---- repeat the 3 doses again, If still fails then HBIG would be required for protection if exposed to virus

Measles

Introduction	• RNA paramyxovirus • Mode of transmission: Respiratory droplets
nical features	• 3 C's Cough, Coryza, Conjunctivitis, then Koplik spots *(grayish-white spots on buccal mucosa)* • Maculopapular rash; starts at head (nape of neck and behind ears) and spreads downward & fades in same manner
Complications	• Otitis media –most common • Bacterial pneumonia also most common complication and the most common cause of mortality. • Encephalitis • Subacute sclerosing panencephalitis (SSPE) -- is a rare late complication
nagement	• Supportive, vitamin A, vaccination (6-9 months of age for infants) • Non immunized persons----vaccination should be done within 72 hours if comes in contact
If the person is exposed to virus	

Age	Management (post-exposure)
0-6 months	• Immune serum globulin if mother is not immune
Pregnant or immunocompromised	• Immune serum globulin
All others	• Vaccine within 72 hours of exposure for susceptible individuals

Varicella Zoster virus (VZV) -----Chicken Pox & Shingles

- **Agent:** VZV—DNA virus
- VZV produces two diseases

Primary infection	Chickenpox (varicella)
Reactivation infection	Shingles (Herpes zoster)

- **Chickenpox**

Introduction	• <u>Agent</u>: DNA virus • Infectivity period: Children with chickenpox are contagious from 24 hours before the onset of rash until all lesions have crusted over (7 days) • Mode of transmission: Congenital: Transmission may occur at any time during the pregnancy. Rash developing within the first 10 days of life is due to in utero infection Neonatal acquired: Infants with mothers who develop varicella lesions anytime from 5 days before delivery to 2 days after delivery are at high risk for severe (fatal) disease Acquired: Respiratory droplets
Clinical features	• Tear drop vesicular rash (intensely itchy/ pruritic rash) that rapidly progress to oval "tear drop" vesicles on an erythematous base (dew drops on a rose petal) • Rash is in a centripetal distribution i.e. more on trunk than on limbs
Complications	• Bacterial superinfection---most common --- (often Staphylococcus aureus) • Pneumonia • Encephalitis • *Reye syndrome (associated with ingestion of salicylates)* • Hepatitis • Infection during pregnancy: ◦ Teratogenic effects (**congenital varicella syndrome**: zigzag scarring of the skin, shortened or malformed extremities, central nervous system damage, and eye abnormalities such as cataracts or Chorioretinitis) ◦ **Severe varicella infection in a neonate may develop if mother acquires varicella within one week of delivery**
Management	Immunocompromised or severe disease-----Consider acyclovir, VZIG and supportive treatment.

- **Shingles (Herpes Zoster)**

Introduction	When a person recovers from chickenpox, the virus remains in the dorsal root ganglion of sensory nerves. VZV when reactivated later in life causes shingles
Clinical features: (mnemonic <u>PDF</u>)	Very **P**ainful **D**ermatomal distribution of rash **F**ever • The rash may last as long as 4 weeks, with pain persisting for weeks or months • **Post herpetic neuralgia** ◦ It refers to the persistent pain for weeks to months following healing of the rash. ◦ Most common complication • **Ramsay Hunt syndrome** ◦ It occurs when virus involves geniculate ganglion. ◦ Presents with facial palsy, ipsilateral loss of taste plus vesicular rash in external auditory canal
Guidelines	• Doubt about mother immunized= check varicella antibodies first if not immune= VZIG (as soon as possible—effective up to 10days post exposure • Oral acyclovir should be given to pregnant women = if present within 24 hours of rash

Mumps

Introduction	• Agent: RNA paramyxovirus Infectivity period: Contagious 1 day before and 3 days after swelling appears Mode of transmission: Respiratory droplets & secretions
Clinical features	• Fever, Swollen salivary glands, especially parotid glands (can be unilateral or bilateral- bilateral more common)
Complications	• **Meningoencephalitis----most common** **Epididymo-orchitis** ◦ Common in adults, but rare before puberty ◦ Affected testis may atrophy but sterility is rare. • Pancreatitis • Oophoritis • Myocarditis & arthritis

H1N1 Influenza

Introduction	• The H1N1 influenza virus (swine flu) is a subtype of the influenza-A virus and the most common cause of flu in humans.
Following are at high risk	• Patients with chronic illnesses and those on immunosuppressants • Pregnant women • Young children under 5 years old
Features	• High grade fever, myalgia, sore throat, cough, diarrhea and vomiting • Minority of patient may develop ARDS
Treatment	• Oral medication-----**Oseltamivir** (Tamiflu)----neuraminidase inhibitor • Inhaled medication-----**Zanamivir** (Relenza)---- neuraminidase inhibitor—**may induce bronchospasm in asthmatics**

Dengue Fever

Introduction	• Causative Agent: Dengue virus (4 serotypes) • Mode of transmission: Bite of Female mosquitoes --**Aedes aegypti (mainly)** & Aedes Albopictus (lesser extent) ◦ Remember: Unlike other mosquitoes Ae. Aegypti is a day-time feeder; its peak biting periods are early in the morning and in the evening before dusk.
Clinical features	• High grade fever- abrupt onset- -continuous fever pattern, Severe headache, Periorbital pain, Muscle and joint pain, Rash • **Dengue hemorrhagic fever & dengue shock syndrome**
Diagnosis	• *Dengue NS-1--- in early stages* *Dengue serology ---IgG and IgM--- in later stages*
Management	• Supportive and symptomatic management

HIV Virus

Cause	• HIV destroys CD4+ cells —weakens immune system • Start antiretroviral theray in HIV when CD4 count is less than $350 \times 10^6/L$	
AIDS	**Transmission**	• Sexually transmitted • Contact with infected blood • From mother to child during pregnancy, childbirth or breast-feeding

Diagnosis	• AIDS diagnosis ≤ 200 CD4+ cells/mm3 (normal : 500-1500 cells/mm3)
Diagnostic Tests	• Presumptive test→ELISA and • Confirmatory: Western blot assay • For viral load→PCR **Note: ELISA/Western blot tests** • Falsely $\ominus$ in the first 1-2 months of HIV infection Fasely $\oplus$ initially in babies born to infected mothers Use PCR in neonates to detect viral load.

Common diseases of HIV-positive adults

Cd4+ cell count < 500/mm3

Candida albicans	*Oral thrush*
EBV	*Oral hairy leukoplakia*
HHV-8	*Kaposi sarcoma*
HPV	*Squamous cell carcinoma, cervical cancer*

Cd4+ cell count < 200/mm3

Pneumocystis jirovecii

Cd4+ cell count < 100/mm3

Aspergillus fumigatus	Hemoptysis→Cavitation /infiltrates on chest imaging
Candida albicans	Esophagitis
CMV	*Retinitis*
Cryptococcus Neoformans	*Meningitis*
Mycobacterium avium	
Toxoplasma gondii	*Brain abscesses*
Cryptospridum	*most common causes of Diarrhea*

- **Cryptosporidium**
  - Symptomatic treatment
  - *For severe cases= Nitzonaxide*
  - Diagnosis= blood culture + bone marrow examination

  Cryptosporidium cysts turn red following acid fast staining
- ***Pneumocystis jirovecii/carinii***
  - *Bilateral interstitial pulmonary infiltrates "Ground-glass-pulmonary infiltrates" opacities on CXR*
  - *Diagnosis= Broncho alveolar lavage **(silver stain shows PJ)***
  - *Management:*
    - *Co-trimoxazole*
    - *IV pentamidine in severe cases*
    - *Steroids if hypoxic*
- **Brain lesions in AIDS**
  - **Toxoplasmosis**→Most common lesion, *Multiple ring enhancing lesions in basal ganglia*
  - **Progressive multifocal leukoencephalopathy**→caused by JC virus, *multiple bilateral non enhancing lesions in white matter*
  - **Primary CNS lymphoma**→No fever, *single large homogenous enhancing periventricular lesion*
- **How to differentiate between toxoplasmosis and lymphoma**
  - **Thallium SPECT test, --- +ive in Lyphoma and -ive in Toxoplasmosis**
- **Cryptococcal meningitis:**
  - IV amphotericin B + Flucytosine for 2 weeks Then fluconazole for 8 weeks

HIV seroconversion

- Hint: Man returns from trip abroad with maculopapular rash and flu like illness- think of HIV seroconversion always
- **For HIV seroconversion---Do HIV PCR and p24 antigen test to confirm diagnosis**

Chapter 3: Parasitology

Gastrointestinal

Organism	Disease	Treatment
Giardia lamblia	**Giardiasis** • bloating, flatulence, foul-smelling, fatty diarrhea	Metronidazole
Entamoeba histolytica	**Amebiasis** • bloody diarrhea (dysentery), liver abscess, **histology shows, flask-shaped ulcer**	Metronidazole
Cryptosporidium	**Severe diarrhea in AIDS**	Supportive Severe cases-Nitazoxanide

CNS infections

Organism	Disease	Treatment
Toxoplasma gondii	**Congenital toxoplasmosis** • Classic triad of Chorioretinitis, hydroCephalus, and intraCranial Calcifications In AIDS **brain abscesses**	Sulfadiazine + pyrimethamine

Hematologic infections

Organism	Disease	Treatment	

Plasmodium (4species)
• P. Vivax
• P. Ovale
• P. Falciparum
• P. Malariae
New specie: P. knowlesi is currently considered as the fifth species causing malaria
P. malariae is associated with nephrotic syndrome
	Malaria
	• fever, headache, anemia, splenomegaly
	• P. Vivax/ovale
	  ◦ 48-hr cycle *(tertian fever*- fever on every 3rd day)
	• P malariae
	  ◦ 72-hr cycle *(Quartan)*
	• P. falciparum
	  Severe; irregular fever patterns; cerebral malaria, hemoglobinuria, black water fever.
		NICE guidelines
		• P. Vivax/ovale or malariae
		  ◦ Chloroquine
		• P. falciparum uncomplicated
		  ◦ artemisin based combinations
		• Sever falciparum malariae
		  ◦ IV artesunate
		  ◦ If parasite count >10% --exchange transfusion
		  ◦ Shock may indicate co-existing bacterial infection—malaria rarely causes hemodynamic collapse
			Features of severe malaria
			• Parasitaemia > 2%
			• Hypoglycemia
			• Severe anemia
			• Cerebral malaria, renal failure, coma
			• *ARDS (P. malariae)*

		Prophylaxis
		• *Chloroquine (1 week before and 4 weeks after travel)*
		• If Chloroquine resistant area
		  ◦ Malarone (atovaquone + proguanil),
		  ◦ Mefloquine (avoid in epilepsy patient),
		  ◦ Doxycycline
		• If children
		  ◦ Diethyltolumide
		  ◦ Doxycycline (if age >12 years)	

Visceral Infections

Organism	Disease	Treatment	
Trypanosoma Cruzi (kissing bug)	***Chagas disease (American trypnosmoiasis)*** • **C**ardiomyopathy, mega**C**olon, megaesophagus • Unilateral periorbital swelling (Romaña sign) characteristic of acute stage	Benznidazole	
Trypanosoma brucei	***African sleeping sickness*** • Lymphadenopathy (**Post cervical**), fever, somnolence/coma	*Suramin /Pentamidine (blood)* *Melarsoprol (CNS)*	Spread by **Tsetse fly**
Leishmania	Leishmania Donovani----**Visceral leishmaniasis** • (kala-azar)--spiking fevers, hepatosplenomegaly, pancytopenia • Kala azar means Black skin---Grey black color skin Leishmania tropica/ Mexicana----**Cutaneous leishmaniasis** Leishmania Brazilleus ----**Mucocutaneous Leishmaniasis**	*Amphotericin B,* *Sodium stibogluconate*	Spread by **Sand flies** Hepatspleenomegaly pancytopenia lymphadenopathy **biopsy=diagnostic**
Trichomonas vaginalis (Sexually transmitted	***Vaginitis*** foul-smelling, *greenish discharge*; itching and burning	Metronidazole for patient and partner (prophylaxis)	

Nematodes (Round Worms)

- Round worms are Bendy so use Bendazoles, except Onchocerca volvulus, Wuchereria bancrofti

Organism	Disease	Treatment
Enterobius vermicularis	*Anal pruritus*	Bendazoles/ Pyrantel pamoate
Ascaris lumbricoides	Biliary obstruction, illeocecal obstruction	Bendazoles
Ancylostoma duodenale	Cutaneous larva migrans • Pruritic, ash from walking barefoot on contaminated beach	Bendazoles / Pyrantel pamoate
Trichinella spiralis	Trichinosis • myalgia • *Transmission is via Undercooked meat (especially pork)*Fever, vomiting, nausea,	Bendazoles
Trichuris trichiura	*Rectal prolapse in children* richinosis	Bendazoles
Onchocerca volvulus	*River blindness*	Ivermectin (**Iver**mectin for **river** blindness
Wuchereria bancrofti	*Elephantiasis* • Worms invade lymph nodes→ inflammation lymphedema	Diethylcarbamazine

Trematodes (flukes)

Organism	Disease	Treatment
Schistosoma	*Squamous cell carcinoma of the bladder* (painless hematuria)	Praziquantel
Clonorchis Sinensis	Biliary tract disease, *Cholangiocarcinoma*	Praziquantel

Cestodes (tapeworms)

Organism	Disease	Treatment
Taenia solium	*Cysticercosis*	Praziquantel
Diphyllobothrium latum	*Vitamin B12 deficiency (megaloblastic anemia)*	Praziquantel
Echinococcus granulosus	*Hydatid cysts* (eggshell Calcification in liver)	Albendazole

Treatment Hints

- Nematodes (**Round** worms) are **Bendy** so use **Bend**azoles, except Onchocerca volvulus, Wuchereria bancrofti
- Trematodes and Cestodes use Praziquantel except Echinococcus granulosus.

Nematode Routes of Infection

Route	Organisms	Mnemonic
Ingested	**E**nterobius, **A**scaris, **T**richinella	You'll get sick if you **EAT** these!
Bite	Ancylostoma	
Cutaneous	**L**oa loa, **O**nchocerca volvulus, **W**uchereria bancrofti	Lay **LOW** to avoid getting bitten

Miscellaneous Topics

Characteristic	Organism
Neutropenic patients	• Candida albicans (systemic), Aspergillus
Periodic Acid Schiff ⊕	• Tropheryma whipplei (Whipple disease)
Pus, empyema, abscess	• S. aureus
Sepsis/meningitis in newborn	• Group B strep
Organ transplant recipient	• CMV
Facial nerve palsy (typically bilateral)	• Borrelia burgdorferi (Lyme disease) ◦ **Lyme disease -----remember erythema chronicum migrans are seen (not erythema marginatum)**
Fungal infection in diabetic or immunocompromised patient	• Mucor or Rhizopus spp.
Hepatitis B virus	• Associated with Polyarteritis nodosa, aplastic anemia
Hepatitis C virus	• Associated with ↑risk B-cell NHL, autoimmune hemolytic anemia
UTI	• Leading causes→E. coli (1st), Staph saprophyticus (2nd), Klebsiella (3rd)

Legionella Pneumophillia	• Causes legionnaire disease
	• **Colonizes water tanks---(questions hints towards air conditioning system or foreign holidays)**
	• Clinical features
	  ◦ Flu like illness
	  ◦ Hyponatremia, Deranged LFT'S
	  ◦ Pleural effusion (30%)
	• Diagnosis
	  ◦ **Urinary antigen test**
	• Management----**Erythromycin**

Animal Bite	• Treatment
	  ◦ Co-amoxiclav
	  If penicillin allergic= then metronidazole + doxycycline

Cat scratch disease	• Caused by bartonella henselae
Septic arthritis (DOC)	• IV Flucloxacillin (clindamycin if penicillin allergic)
Orf	• Exanthemous disease caused by a parapox virus and occurring primarily in sheep and goats, it can be transmitted to humans • In animals ----Scabby mouth • In Humans---- affects hands and arms, initially small papules and later increases and becomes hemorrhagic

Vaginal discharges

Bacterial vaginosis	• *Caused by gardnerella vaginalis*
	Vaginal discharge: "fishy", offensive
	Results in low birth weight, preterm labor, late miscarriage
	Amsels criteria for diagnosis (3 of following 4 points should be present)
	  ◦ *Thin, white/grey fishy discharge*
	  ◦ Stippled vaginal epithelial cells on microscopy
	  ◦ Vaginal pH >4.5
	  ◦ Positive whiff test (addition of K-OH results in fishy odour

	• Treatment: • Oral metronidazole for 5-7 days (alternative topical metronidazole or clindamycin)
Trichomonas vaginalis	• *Yellow/green, frothy discharge, strawberry cervix,* itchy and burning Metronidazole for patient and partner (prophylaxis)
Candida	• *Cottage cheese discharge,* vulvitis, itchy

Genital lesions

	Granuloma Inguinale (Aka Donovansois)	Chancroid	Lymphogranuloma Venerum
Caused by	Klebsiella granulomatosis	Hemophilus ducreyi	Chlaymdia trachomatis
Features	Painless ulcers	**Painful ulcers (U cry with docreyi—note--painful ulcers also seen with herpes)**	Painless ulcer
Treatment	Painless ulcers	Single dose of azithromycin or IM ceftriaxone	Doxycycline or Erythromycin

Incubation Periods

Less than 1 week (Mnemonic—**MIDS**)'	1-2 weeks (Most common presenting fever diseases in OPD)	2-3 weeks (**MMR**----replace the measles with **chicken pox**)	Longer than 3 weeks (3 words---**HIV**)
• **M**eningococcus • **I**nfluenza • **D**iphtheria • **S**carlet fever	• Malaria • Dengue • Typhoid • Measles	• **M**umps • **C**hickenpox • **R**ubella	• **H**IV • **I**nfectious mononucleosis • **V**iral hepatitis • **C**MV (**C**ee-3 words)

Normal flora

Location	Organisms
Skin	*S. epidermidis*
Nose	*S. epidermidis;*
Oropharynx	*Viridans group streptococci*
Dental plaque	*S. mutans*
Colon	*B. fragilis > E coli*
Vagina	*Lactobacillus, colonized by E coli and group B strep*

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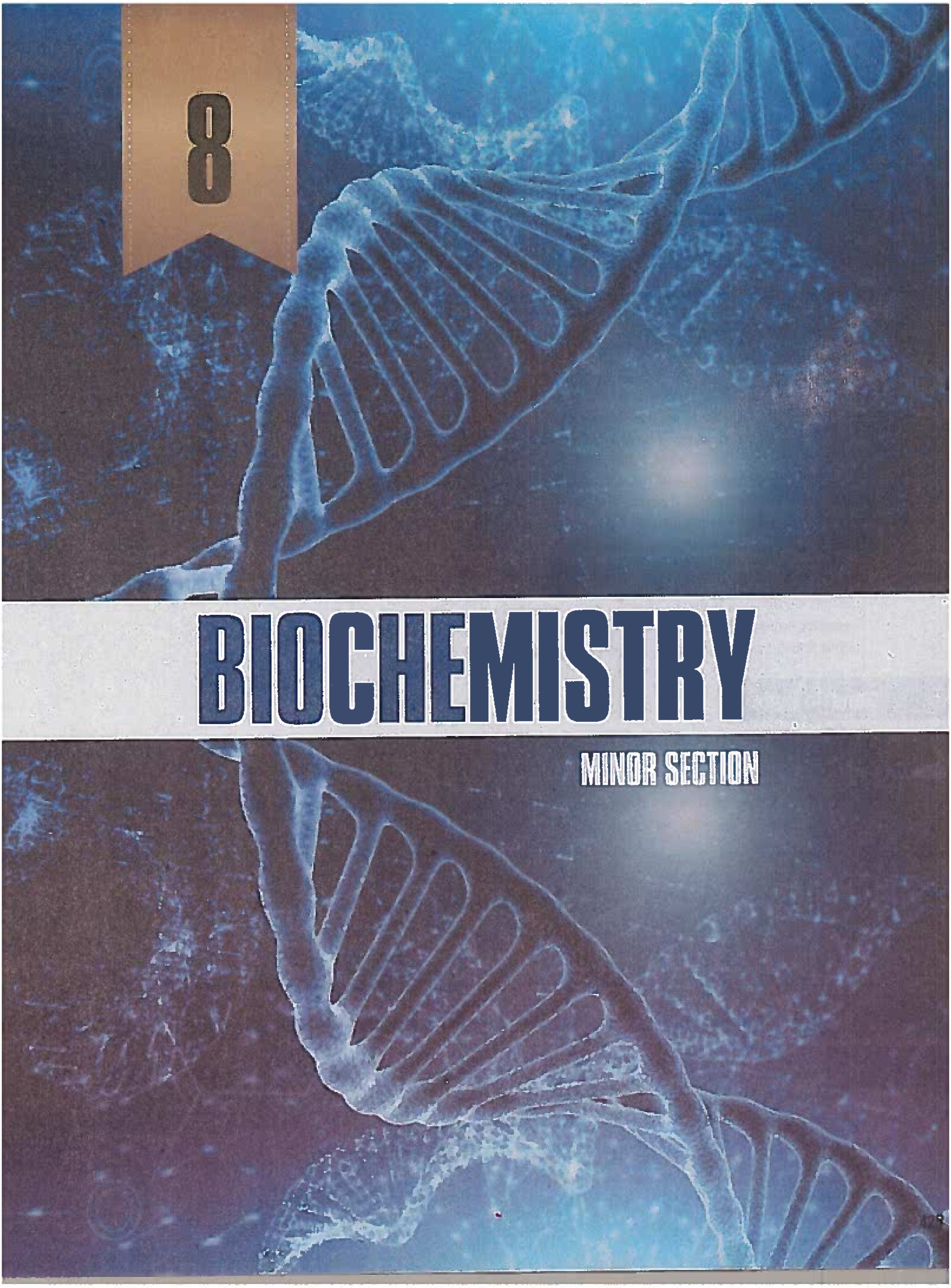


8

BIOCHEMISTRY

MINOR SECTION

Chapter 4: Biochemistry

Structural Biochemistry of Nitrogenous Bases/Nucleic Acid

Nitrogenous Bases

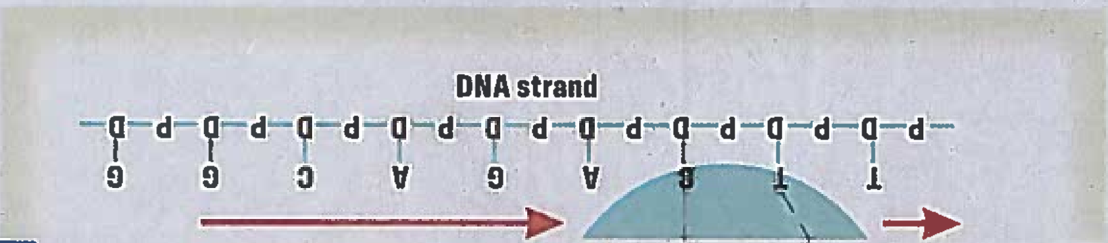
- These are Bases which take part in formation of nucleic acids (DNA and RNA).
- Two types:
    - **PUR**ines: includes **A**denine and **G**uanine (**PURE As Go**ld)
    - **PY**rimidines: include **C**ytosine, **U**racil and **T**hymines (**C,U,T** THE **PY**(pie)

      Note: In RNA, thymine is replaced by uracil.
- Cytosine makes pair with Guanine, while adenine makes pair with thymine
    - **C-G, A-T.** (mnemonic—**C**ol**GAT**e)
- There are 3 H-bonds between C-G, and 2 H bonds between A-T
    - Mnemonic to remember (**CEE** and **GEE**- **3** letters so **3** bonds)

NucleoSide→Nitrogenous bases + pentoSe sugar (deoxyribose or ribose).
NucleoTide→One of the four nitrogenous bases + pentose sugar + phosphaTe
Nucleic Acid→Combination of many nucleotides e.g. DNA AND RNA.

Genetic Code

- When the two strands of a DNA molecule are split apart, this exposes the purine and pyrimidine bases projecting to the side of each DNA strand.
- It is these projecting bases that form the genetic code.
- The genetic code consists of successive "triplets" of bases—that is, each three successive bases is a code word.
- E.g. in Figure, reading from left to right, has the genetic code GGC, AGA, CTT



Genome

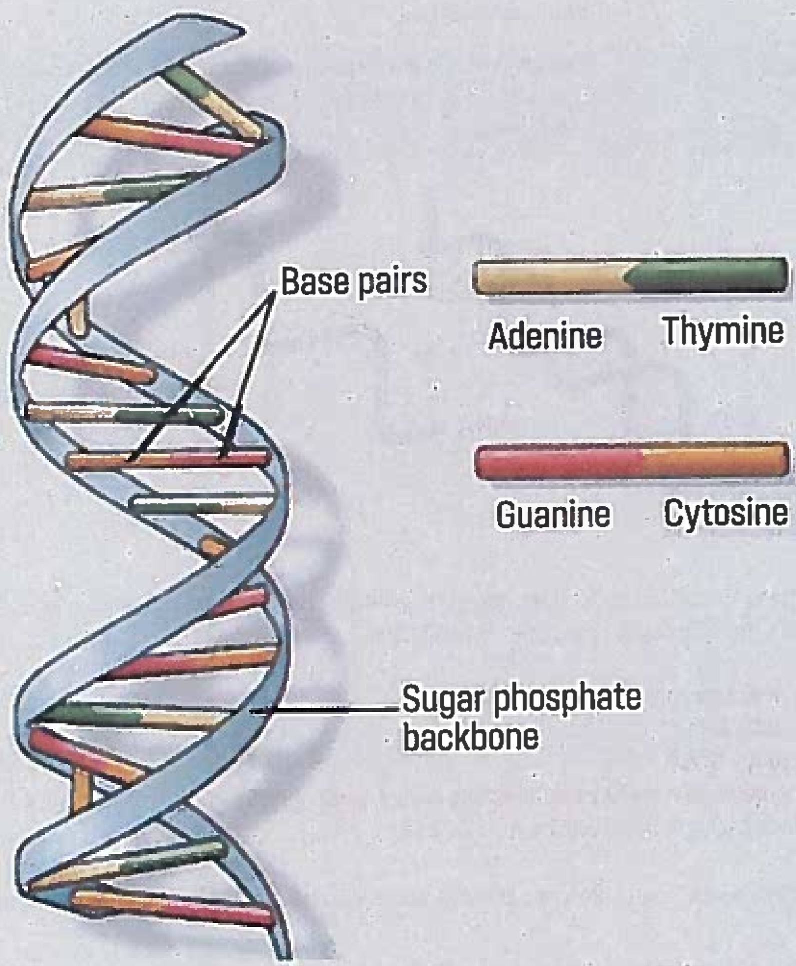
→The hereditary information that is encoded in DNA is called genome.

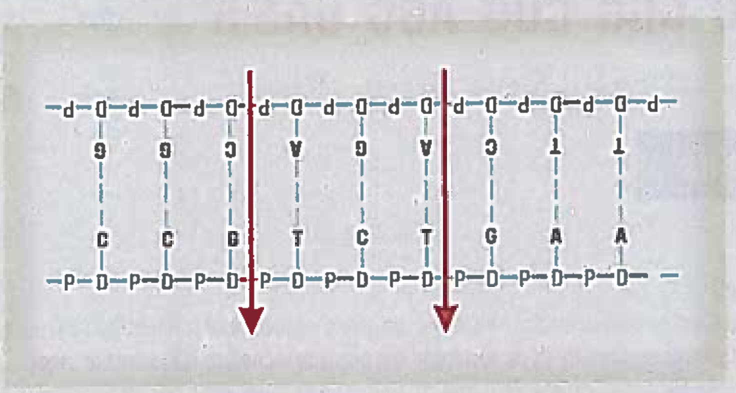
Gene

- Gene is a portion of DNA molecule that contains the message or code for the synthesis of a specific protein from amino acids
- Gene region:
    - **Exons:** *it is the coding region of gene.*
    - **Introns:** *it is the non-coding regions.*

Deoxyribonucleic Acid (DNA)

- *Double stranded*
- *It is formed by deoxyribose, phosphoric acid and four types of bases(A=T, G≡C)*
- Multiple nucleotides are bound together to form two strands of DNA.
- Each DNA strand is comprised of alternating phosphoric acid and deoxyribose molecules as shown in fig below.
- Purine and pyrimidine bases are attached to the sides of the deoxyribose molecules.
- Then, by means of loose hydrogen bonds (dashed lines) between the purine and pyrimidine bases, the two respective DNA strands are held together.
- Each purine base adenine of one strand always bonds with a pyrimidine base thymine of the other strand.
- And each purine base guanine always bonds with a pyrimidine base cytosine.
- Which are twisted around one another in the form of a double helix.
- *Ten pairs of nucleotides are present in each full turn of the helix in the DNA molecule*



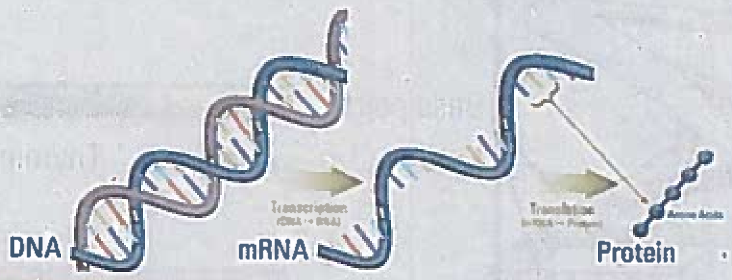


Ribonucleic Acid (RNA)

- *Single stranded.*
- It is formed by ribose, phosphoric acid and four types of bases,
- *RNA is formed from DNA.*
- *Similar to DNA but contains ribose instead of deoxyribose in DNA, and contains uracil instead of thymine.*

Types of RNA

Messenger RNA (m-RNA)	• Messenger RNA carries the genetic code of the amino acid sequence for synthesis of protein from the DNA to the cytoplasm • Messenger RNA molecules are long, single RNA strands that are suspended in the cytoplasm and contains codon
Transfer RNA (t-RNA)	• Transports activated amino acids to the ribosomes to be used in assembling the protein molecule
Ribosomal RNA (r-RNA)	• Ribosomal RNA is present within the ribosome and forms a part of the structure of ribosome. It is responsible for the assembly of protein from amino acids in the ribosome



Codons and Anti-Codon

The Codons:

- Sequence of three successive nucleotides (triplet) in m-RNA corresponding to genetic code in of DNA is called a codon.
- *Total 64 codons, out of which 61 code for amino acids and 3 are stop codons*
- *Stop codons are*
    - **UAA (U A**re **A**way)
    - **UGA (U G**o **A**way)
    - **UAG.(U A**re **G**one)
- ***AUG coding for methionine is a starting (initiating codon).*** (**AUG**=in**AUG**uarates protein synthesis)
- Protein synthesis begins with methionine in eukaryotes.

The Anticodon:

- *Sequence of three successive nucleotides in t-RNA corresponding to codon is called an anti-codon*

5' AUG CAA CCC GAC UCC AGC 3' ← **Codon**

3' UAC GUU GGG CUG AGG UAG 5' ← **AntiCodon**

Met--Gln---Pro---Asp--Phe--Ser ← **Amino Acids**

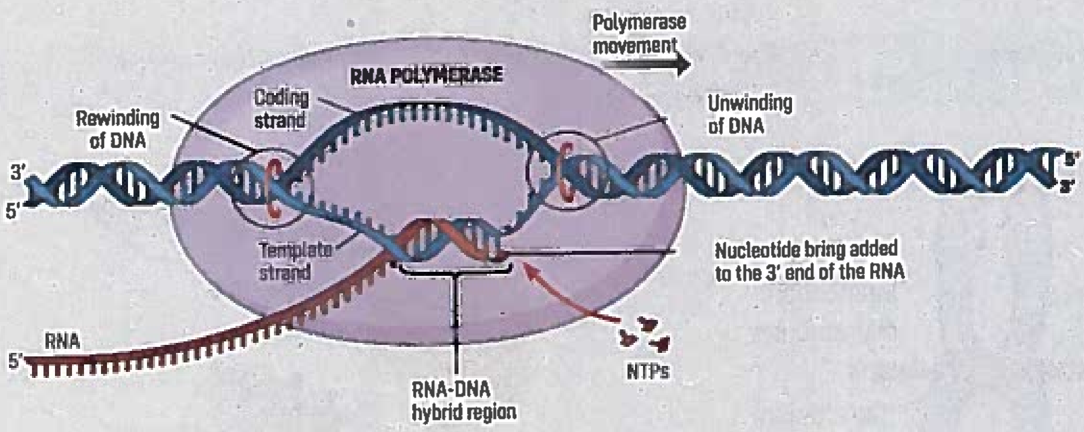
Synthesis of Proteins

Two steps

Transcription:

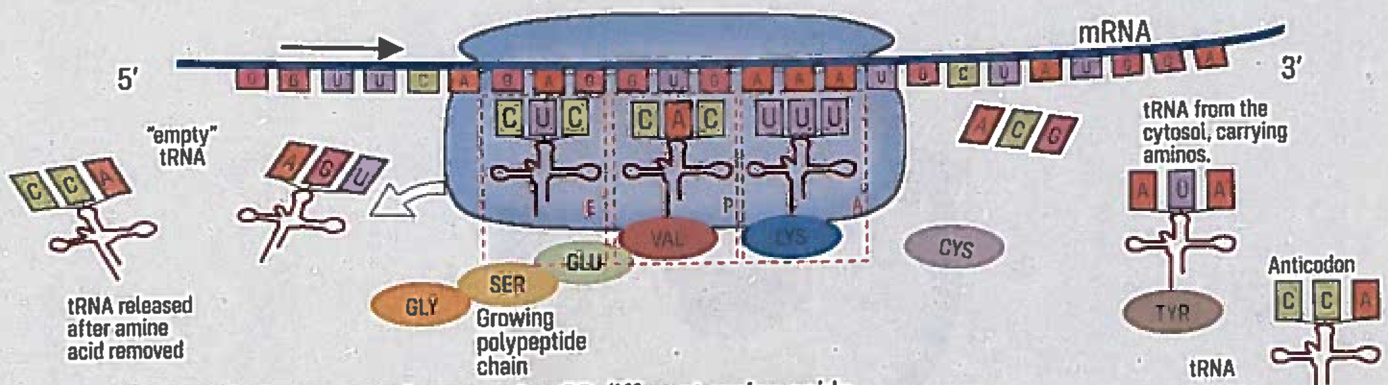
- *It occurs in nucleus*
- In the DNA strand immediately ahead of the initial gene is a sequence of nucleotides called the promoter.
- The RNA polymerase recognizes this promoter and becomes attached to it.(essential step)
- *Then the polymerase moves along the DNA strand, temporarily unwinding and separating the two DNA strands at each stage of its movement by enzyme Helicase*

- It adds at each stage a new activated RNA nucleotide to the end of the newly forming RNA chain.
- At some stage RNA
- polymerases encounters chain-terminating sequence; this causes the polymerase and the newly formed RNA chain to break away from the DNA strand.
- Then the polymerase can be used again and again to form still more new RNA chains.
- New RNA strand has weak hydrogen bonds with the DNA template and DNA has high affinity for rebounding with its own complementary DNA strand.
- Thus, the RNA chain is forced away from the DNA and is released into the nucleoplasm
- Thus, the code that is present in the DNA strand is eventually transmitted in complementary form to the RNA chain.



Translation:

- *It occurs in cytoplasm.*
- *It is the process by which the mRNA is read by ribosome to produce a protein.*
- The mRNA moves out of nucleus into the cytoplasm.
- Now, a group of ribosomes called polysome gets attached to mRNA.
- The sequence of codons in mRNA are exposed and recognized by the complementary sequence of base in tRNA. The complementary sequence of base is called anticodon.
- According to the sequence of bases in anticodon, different amino acids are transported from the cytoplasm into the ribosome by tRNA that acts as a carrier.
- With the help of rRNA, the protein molecules are assembled from amino acids.
- The protein synthesis occurs in the ribosomes which are attached to rough endoplasmic reticulum

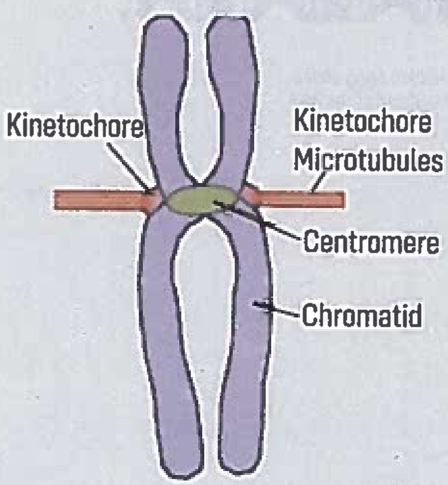


The translation process incorporates 20 different amino acids in the precise sequence dictated by the three-base condons builds the polypeptide chains tha wil become proteins.

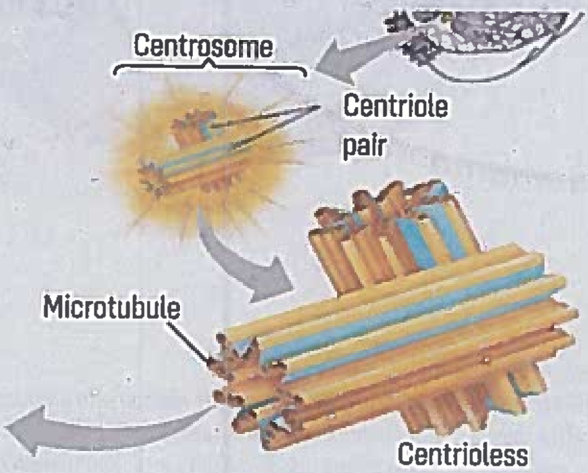
Cell Cycle

Some Terms to Know Before Cell Cycle

Centromere	• Part of a chromosome that links sister chromatids
Kinetochore	• Is a protein structure on chromatids where the spindle fibers attach during cell division to pull sister chromatids apart
Centriole	• Small cylindrical body consisting mainly of nine parallel tubular structures arranged in the form of a cylinder.
Centrosome	• Each pair of centrioles, along with attached pericentriolar material, is called a centrosome
Mitotic apparatus	• Entire set of microtubules plus the two pairs of centrioles is called the mitotic apparatus



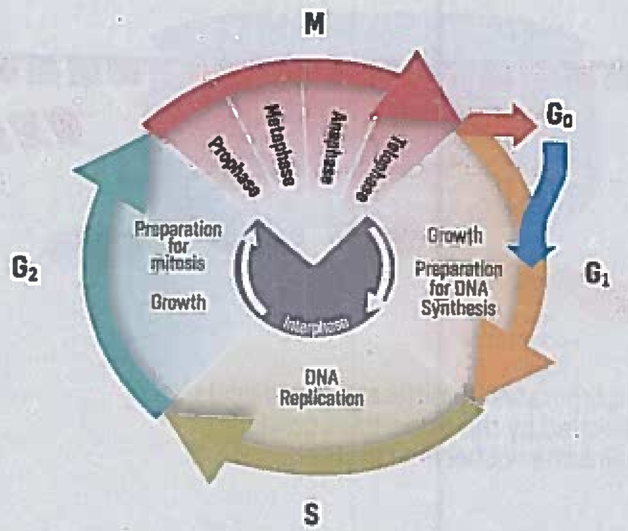
Detail of Chromosome



9 sets triplet microtubules

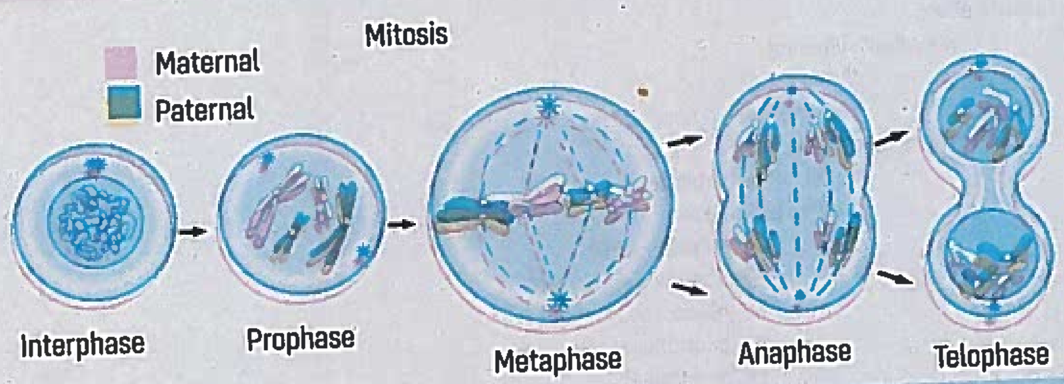
Cell cycle

Divided into 3 phases

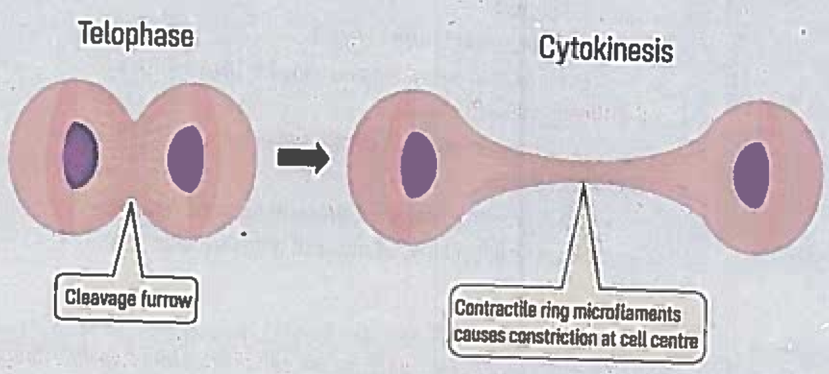


Interphase	• Gap 1 (G1 phase)
	  ◦ Cells increase in size in Gap 1.
	  ◦ Ensures that everything is ready for DNA synthesis.
	• Synthesis phase (S phase):
	  ◦ DNA replication (DNA synthesis) occurs during this phase.
	• Gap 2 (G2 phase):
	  ◦ G2 is interval between DNA synthesis and mitosis.
	  ◦ Most radiosensitive along with mitosis phase

Mitosis phase	• *Mitosis is a process in which parent cell divides into two new daughter cells.*
	• *The daughter cell contain same number and type of chromosome as in parent cell.*
	• It has the following stages
	  ◦ Prophase:
	    ➢ The chromosomes of the nucleus become condensed into well-defined chromosomes.
	    ➢ Nucleolus within the nucleus dissolves
	  ◦ Prometaphase:
	    ➢ Nuclear membrane is disrupted giving microtubules access to the chromosome.
	    ➢ Kinetochores assemble at each centromere on the chromosome.
	    ➢ Certain microtubules bind to kinetochore
	  ◦ Metaphase:
	    ➢ Attached microtubules start pulling chromosomes towards opposite ends of the cell.
	    ➢ The resulting tension causes the chromosomes to align at the metaphase plate.
	  ◦ Anaphase:
	    ➢ The kinetochores separate, and chromosomes moves to opposite side
	  ◦ Telophase:
	    ➢ Reversal of prophase and Prometaphase events.
	    ➢ The nuclear envelop re-forms.
	    ➢ Chromosomes decondense or relax to form chromatin.
	    Mitosis is complete. Each daughter nucleus has an identical set of chromosomes



Cytokinesis	• Cytoplasm divides through the process of cleavage. • Cleavage furrow forms around the centre of cell. • A contractile ring forms at the furrow. • The ring is composed of actin and myosin



Mutations in DNA

- A mutation is a permanent change in the DNA sequence of a gene
- Can be inherited or acquired.
- Mutations in DNA Severity of damage
  - *frameshift > nonsense > missense > silent*

Silent	• Nucleotide substitution but codes for same (synonymous) amino acid
Missense	• Nucleotide substitution resulting in changed amino acid • E.g. Sickle cell disease (substitution of glutamic acid with valine).
Nonsense	• Nucleotide substitution resulting in early **stop** codon (UAG, UAA, UGA). • Usually results in non-functional protein. ◦ Mnemonic: Stop the nonsense
Frameshift	• Deletion or insertion of a number of nucleotides not divisible by 3 resulting in misreading of all nucleotides downstream. • Protein may be shorter or longer, and its function may be disrupted or altered. • E.g. Duchenne muscular dystrophy, Tay-Sachs disease

Vitamins

- Classification:
  - Fat soluble vitamins
    - Vitamin A, D, K, E
    - Toxicity more common than for water-soluble
  - Water soluble vitamins
    - Vitamin C (ascorbic acid)
    - Vitamin B complex
      - B1 (thiamine: TPP)
      - B2 (riboflavin: FAD, FMN)
      - B3 (niacin: NAD+)
      - B5 (pantothenic acid: CoA)
      - B6 (pyridoxine)
      - B7 (biotin)
      - B9 (folate)
      - B12 (cobalamin)
    - *All wash out easily from body except B12 and B9 (folate).*
    - *B12 stored in liver for 3-4 years.*
    - *B9 stored in liver for 3-4 months.*

Vitamin	Uses	Deficiency
Vitamin A	• *Essential for normal differentiation of epithelial cells* • *Prevents squamous metaplasia* • *Used to treat measles and Acute promyelocytic leukemia*	• Dry skin • *Night blindness* • Corneal degeneration • *Bitot spots* • *In excess: teratogenic*
Vitamin B1 (thiamine)	• Cofactor for enzyme reactions	• **Wernicke-korsakoff syndrome:** ***Confusion, Ataxia, Nystagmus, Ophthalmoplegia, Memory loss*** Mnemonic: Wernicke problems come in a **CAN O'** beer. • **Dry beriberi:** *polyneuritis, symmetrical muscle wasting* **Wet beriberi:** *high cardiac output failure (dilated cardiomyopathy)*
Vitamin B2 (Riboflavin)	• Component of flavin FAD and FMN • B2= gives two ATP by FAD and FMN	• *2 C's : Cheilosis and Corneal vascularization*
Vitamin B3 (Niacin)	• Component of NAD and NADP. • *Derived from tryptophan* • *Synthesis requires VIT B_2 AND B_6* • B3 = 3 ATP • Used to treat dyslipidaemias	• *Hartnup disease:* • *Pellagra: 3D's:*
Vitamin B5 (Pantothenic acid)	• *Component of co-enzyme A*	• Dermatitis, alopecia
Vitamin B6 (Pyridoxine)	• Required for synthesis of heme, histamine, and neurotransmitter like GABA and dopamine	• *Peripheral neuropathy* • Convulsions • *Sideroblastic anemia*
Vitamin B7 (Biotin)	• Cofactor for carboxylation reactions • Act as cofactor in oxidation of fatty acids	
Vitamin B9 (Folate)	• *Converted to THF acid,* important for synthesis of nitrogenous bases in DNA and RNA • *Found in leafy vegetables* • *Absorbed in jejunum*	• *Deficiency causes macrocytic megaloblastic anemia.* • Most common vitamin deficiency seen in US. • Seen in alcoholism and pregnancy • Deficincey in early pregnancy causes neural tube defects in newborn.
Vitamin B12 (cobalamin)	• *Found in animal products* • *Large reserve pool 3-4 years in liver* • *Deficiency caused by malabsorption (eg, sprue, enteritis, Diphyllobothrium latum), lack of intrinsic factor (pernicious anemia, gastric bypass surgery).*	• *Macrocytic megaloblastic anemia* • *Paresthesias* • *Subacute combined degeneration of spinal cords due to abnormal myelin*
Vitamin C (Ascorbic acid)	• Anti-oxidant • *Facilitates iron absorption* • Necessary for hydroxylation of proline and lysine in collagen synthesis Converts dopamine to NE	• *Scurvy due to Collagen synthesis defect*

Vitamin D	• Vitamin D forms: · D2 = ergocalciferol—ingested from plants. · D3 = cholecalciferol—consumed in milk, formed in sun-exposed skin (stratum basale). · *25-OH D3 = storage form.* · *1, 25-(OH)$_2$ D3 (calcitriol) = active form.* • ↑ intestinal absorption of Ca++ • ↑ bone mineralization at low levels • ↑ bone resorption at high levels	• *Rickets (children)* • *Osteomalacia (adults)* • *Breast fed infants should receive oral vitamin D.*
Vitamin E (tocopherol)	• Anti-oxidant • *Can enhance the anti-coagulant effect of warfarin*	• Muscle weakness. • *Neurologic presentations like B12 deficiency* • Hemolytic anemia
Vitamin K (K is for Koagulation)	• *Blood clotting* • *Synthesized by intestinal flora* • *Necessary for maturation of factors 2, 7, 9, 10 and protein c and s*	• *Neonatal Hemorrhage* (Neonatal hemorrhage with ↑ PT and ↑ aPTT but normal bleeding time)
Zinc	• Essential for activity of 100+enzymes	• *Delayed wound healing* • Hypogondisam • ↓ adult hair (axillary, facial, pubic)

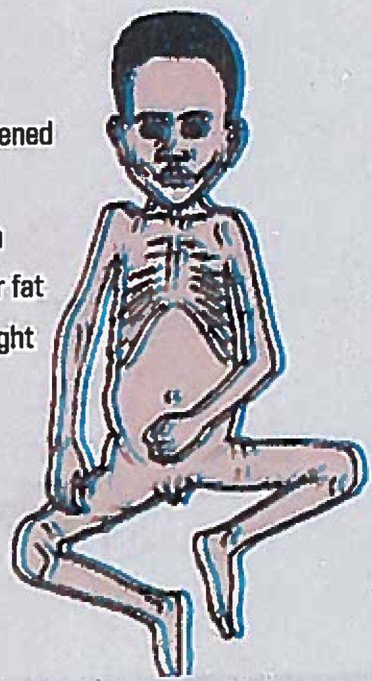
Protein-Energy Malnutrition

Kwashiorkor	Marasmus
• Protein malnutrition resulting in *skin lesions,* Edema due to ↓ plasma oncotic pressure liver malfunction (fatty change due to ↓ apolipoprotein synthesis).	• Marasmus is protein-energy malnutrition (PEM) not causing edema • Diet is deficient in calories but no nutrients are entirely absent.
• *Moon face*	• *Old man appearance*
• *Mild retardation*	• *Severe retardation*
• *Abdomen is protuberant*	• *Abdomen in shrunken*
• Clinical picture is small child with swollen abdomen	• Clinical picture is that of a child who looks like an old man
• Mnemonic: Kwashiorkor results from protein deficient **MEALS** · o**M**alnutrition · o**E**dema · o**A**nemia · o**L**iver (fatty) · **S**kin lesions (hyperkeratosis/ hyperpigmentation)	• Mnemonic: **M**arasmus results in **M**uscle wasting

kwashiorkor

- swelling of legs (oedema)
- sparse hair
- moon face, with little interest in surroundings
- falky apperance of skin
- swollen abdomen
- thin muscels, but fat present

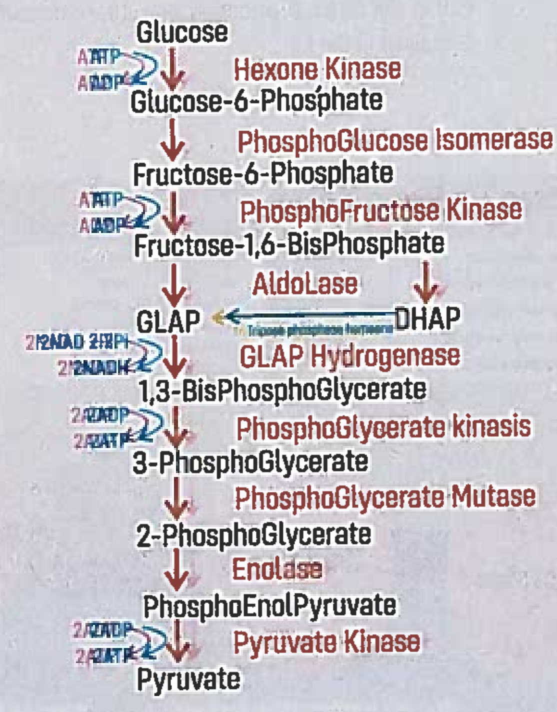
marasmus



- normal hair
- old man or wizened appearance
- thin limbs with little muscle or fat
- very underweight body

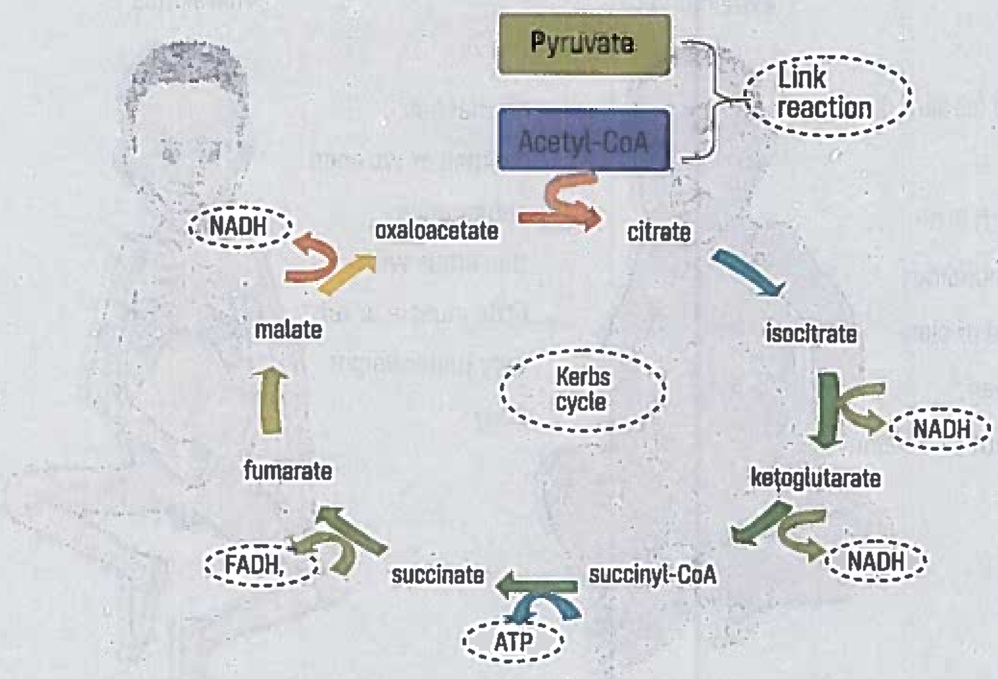
Glycolysis

- Glycolysis pathway that converts glucose $C_6H_{12}O_6$, into pyruvate.
- *Key Rate limiting enzyme is*
    - *Phosphofructokinase*
- *Net product in aerobic glycolysis→Pyruvate*
- *Net product in anaerobic glycolysis→Lactate*
- Pyruvate then enters the Krebs citric acid cycle



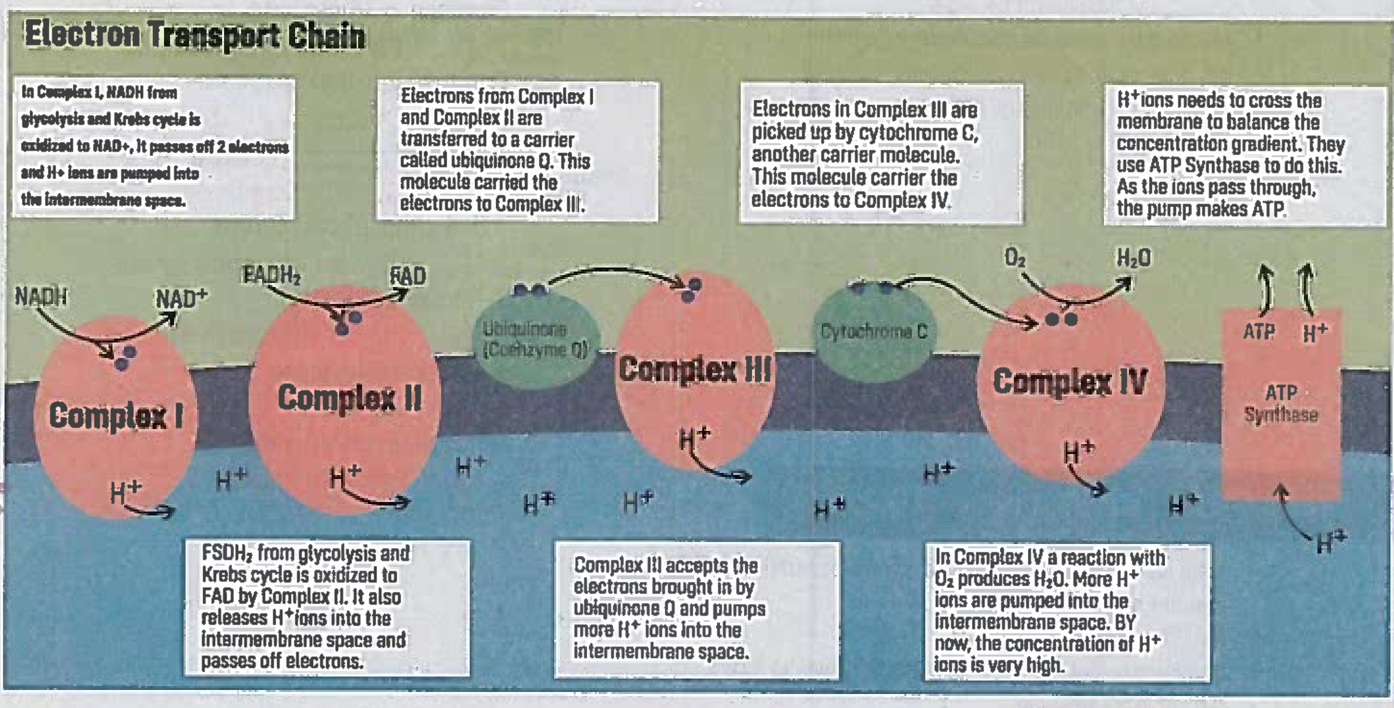
Krebs Citric Acid Cycle or TCA cycle

- Main and central cycle for the oxidation of carbohydrate, proteins and lipids
- No ATP is utilized in this cycle
- Complete oxidation of one acetyl Co-A yields 12 ATP's.
- *Rate limiting enzyme*
    - *Isocitrate dehydrogenase*, (which converts Isocitrate to α-ketoglutarate)



Electron Transport Chain

- The electron transport chain (aka ETC) is a process occurring in mitochondria, in which the NADH and [$FADH_2$] produced during glycolysis, β-oxidation, and other catabolic processes are oxidized thus releasing energy in the form of ATP
- Explained in the fig



Key Enzymes/ Rate Limiting Steps

Glycolysis (Breaking Of Glucose)	*Phosphofructokinase*
Gluconeogenesis (Forming New Glucose)	*Fructose-1,6-bisphosphatase (F-1,6-BP)*
Glycogenesis (Forming Of Glycogen)	*Glycogen synthase*
Glycogenolysis (Breaking Of Glycogen)	*Glycogen phosphorylase*
TCA cycle	*Isocitrate dehydrogenase.*
HMP shunt	*Glucose-6-phosphate dehydrogenase (G6PD)*
Urea Cycle	Carbamoyl phosphate synthase I
Cholesterol Synthesis	HMG-CoA reductase (inhibited by statins)

Location of Metabolism Pathways

Mitochondria	➢Fatty acid oxidation (β-oxidation), acetyl-CoA production, TCA cycle, oxidative phosphorylation, ketogenesis
Cytoplasm	➢Glycolysis, HMP shunt, and synthesis of steroids(SER), proteins (ribosomes, RER), fatty acids, cholesterol, and nucleotides
Both **Mnemonic: HUGs** take **two** (ie, both)	➢Heme synthesis, Urea cycle, Gluconeogenesis.

Amino Acids

Essential Aminoacids	Non-Essential Amino Acids
Mnemonic: PriVaTe TIM HALL	Mnemonic: Almost All Girls Go Crazy After Getting Proper Shopping Time
• Phenylalanine	• Alanine
• Valine	• Asparagine
• Threonine	• Glycine
• Tryptophan	• Glutamate
• Isoleucine	• Cysteine
• Methionine	• Aspartate
• Histidine	• Glutamine
• Arginine	• Proline
• Leucine	• Serine
• Lysine	• Tyrosine

Glucogenic aminoacids Mnemonic: I met his valentine, she is so sweet (glucogenic).	• Methionine (**Met**) • Histidine (**His**) • Valine (**Val**).
Acidic Aminoacids	• Aspartic Acid (Asp) And Glutamic Acid (Glu).
Basic aminoacids **Mnemonic:** **His lys** (lies) **are basic.**	• Histidine (**His**) • Lysine (**Lys**) • Arginine (**Arg**)-----Most **Basic** Of All
Ketogenic aminoacids **Mnemonic:** (Losers)	• Leucine • Lysine

Fatty Acids

Essential fatty acids\	Non-Essential Fatty Acids
Cannot be synthesized in body must be obtain from diet • *Linoleic acid* • *Linolenic acid*	• Acetic acid • Propionic acid • Butyric acid • Stearic acid • Caproic acid

Metabolic Fuel Use

- *1g carb = 4 kcal*
- *1g protien = 4 kcal*
- *1g alcohol = 7 kcal*
- *1g fatty acid = 9 kcal*

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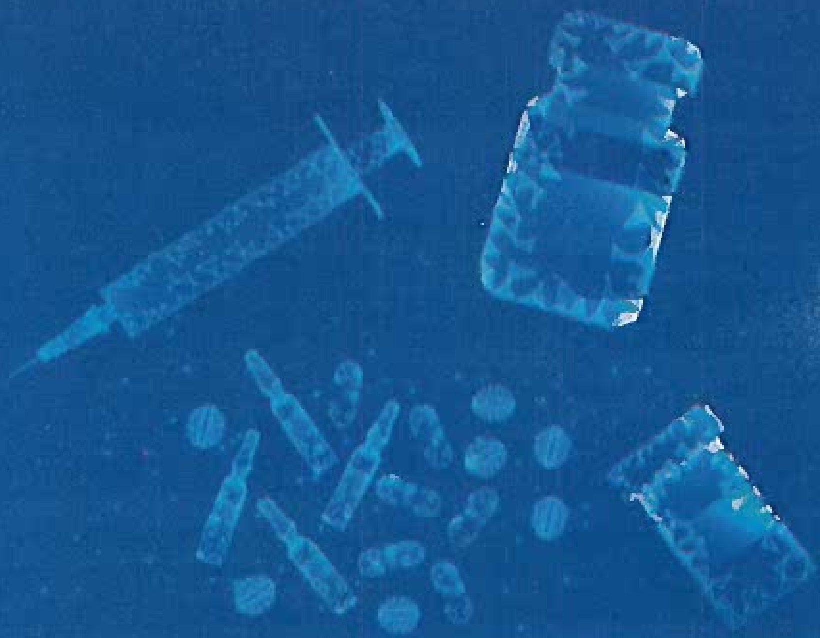
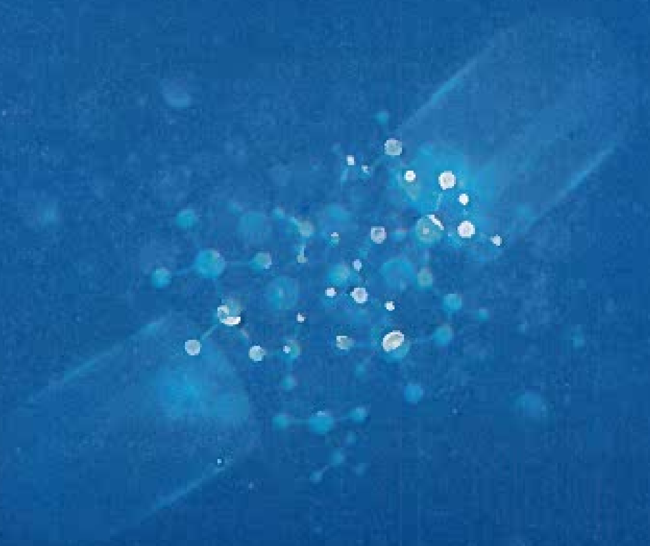
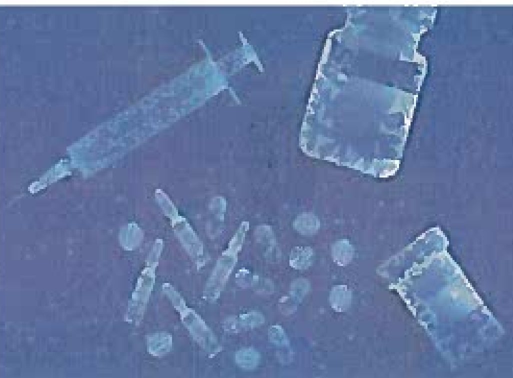


PHARMACOLOGY

MINOR SECTION





Chapter 1: General Pharmacology

Pharmacodynamics:

- *Defined as→action of drug on the body (PharmacoDynamics= Drug action on body)*

Pharmacokinetics:

- *Defined as action of body on the drug*

Volume of Distribution (Vd)

- Defined as relationship between amount of drug in the body to concentration of drug in plasma or blood.
- $Vd = \frac{\text{(Amount of drug in the body)}}{\text{(Plasma drug concentration)}}$
- Depends upon
  - Degree of Plasma protein binding and binding to other tissues within the body

Bioavailability

- Defined as Fraction of administered drug reaching systemic circulation unchanged.
  - For an IV dose, bioavailability = 100%.
  - For Oral dose, bioavailability = < 100% due to incomplete absorption and first-pass metabolism.
- E.g. A drug of 100mg is administered orally, and 70mg of this drug is absorbed unchanged then bioavailability is 70%

Biotransformation/Metabolism of Drugs

- The series of chemical alterations of a drug that occurs within the body is called biotransformation or metabolism of drug.
- This shows how the activity of a drug is altered or terminated

Sites:

- Major site is liver, while other organs involved are kidneys, GI tract, skin and lung

Phases of Biotransformation

- Phase I reactions involve
  - Oxidation reactions (cytochrome P-450 dependent)
  - Oxidation (cytochrome P-450 independent)
  - Reduction
  - Hydrolysis
- Phase II reactions involve
  - Conjugation of drug with certain acid radical or aminoacids. (so that the drug may become polar to be excreted by kidneys)
  - Conjugation involves
    - Methylation, Glucuronidation, Acetylation, Sulfate conjugation

      Note: Patients who are slow acetylators have↑side effects from certain drugs because of ↓rate of metabolism

Elimination of drugs

- Drug in the free form and in the form of their degradation products are eliminated through one or more of the following channel of excretion
    - Renal excretion
    - Lungs e.g. volatile anesthetics as well as gaseous drug product etc.
    - Alimentary system e.g. morphine excreted in bile

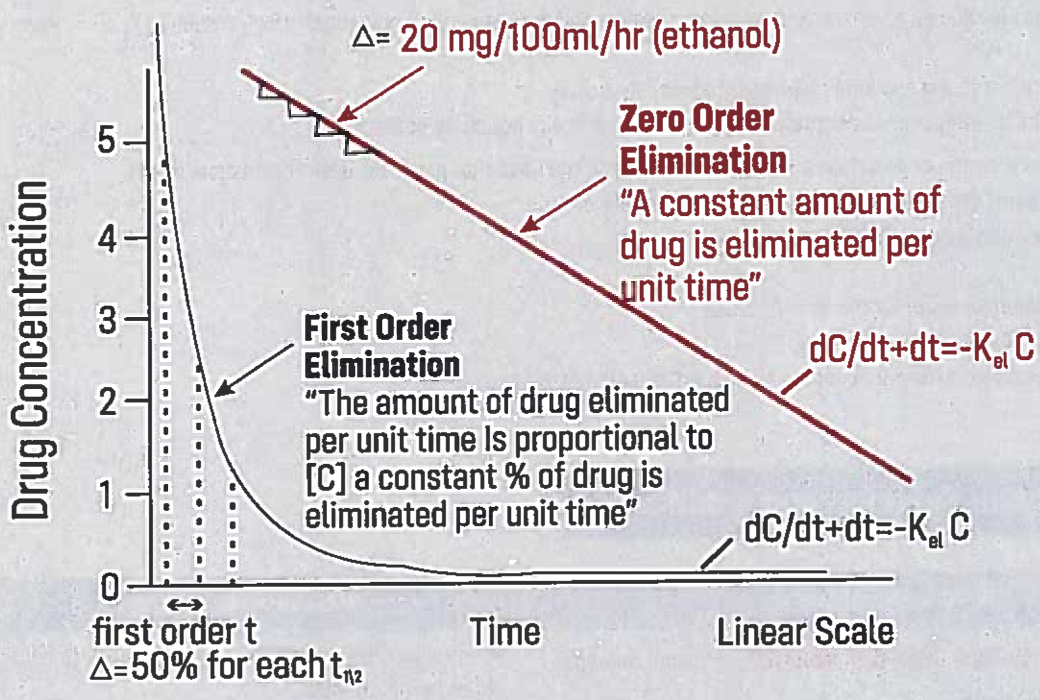
Zero-Order Elimination

- Constant amount of drug eliminated per unit time—**Conc. Decreases in linear fashion**
  No fixed half-life, because higher the dose more the time it would take to clear drug from plasma
    - conc decreases as 100mg→80mg→60mg→40mg
    - constant amount is eliminated, NO fixed half life
- Very few substances are eliminated by zero-order elimination
- Example: (mnemonic----A PEA is round, shaped like the "0" (zero-order))
    - Phenytoin, Ethanol, and Aspirin(Salicylates)

First-Order Elimination

- Rate of elimination is directly proportional to the drug concentration
- i.e. constant fraction of drug eliminated per unit time.---**conc. decreases exponentially with time**
- Concentration of drug decreases by 50% for every half-life
    - conc decreases as 100mg50mg25mg12.5mg
    - constant fraction is eliminated, 50% with each half life

- Most drugs follow first order



Clearance of Drug (CL)

- Clearance (CL) The volume of plasma cleared of drug per unit time.
- Clearance may be impaired with defects in cardiac, hepatic, or renal function.

$$CL = \frac{CL = \text{(rate of elimination of drug)}}{\text{(plasma drug concentration)}}$$

Half-life ($t_{1/2}$)

- It is the time required to eliminate half of the drug either from plasma or body.
- It is expressed as

Half-life ($t_{1/2}$)

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- It is expressed as

$$t_{(1/2)}=\frac{(0.693 \times Vd)}{CL}$$

Types of Drug Interactions

- Addition
  - Effect of substance A and B together is equal to the sum of their individual effects
  - e.g. 1+1 = 2
- Synergism
  - Effect of substance A and B together is greater than the sum of their individual effects
  - e.g. 1+1= more than 2
- Potentiation
  - A drug lacking an effect of its own, but increases the effect of second active drug
  - e.g. 0+1= more than 1

Potency

- it refers to the concentration or dose of a drug required to produce 50% of that drug maximal effect
- it is also known as effective dose concentration, and is a measure of how much drug is required to elicit a response

Efficacy

- It refers to the maximal response produced by a drug
- Clinical effectiveness of drug depends upon its efficacy not on its potency

- It is the ratio of dose that produces toxic effect to the dose that produces desirable clinical effect.
- Greater the therapeutic index greater the safety of drug

Therapeutic index= $\frac{\text{(Toxic dose)}}{\text{(Effective dose)}}$

- *Lithium has narrow therapeutic index*

Therapeutic window

- The range between minimum clinical effect and maximum toxic effect

P450 enzyme inducers and inhibitors

P450 enzyme inducers	P450 enzyme inhibitors
Mnemonic: BullShit CRAP GPS INDUCES (inducers) my rage	Mnemonic: VICK'S FACE All Over GO STOPS (inhibitors) ladies in their tracks
• Barbituates • St. John's wort • Carbamazepine • Rifampin • Alcohol (chronic) • Phenytoin • Griseofulvin • Phenobarbital • Sulfonylureas	• Valproate • Isoniazid • Cimetidine • Ketoconazole • Sulfonamides • Fluconazole • Alcohol (acute) • Chloramphenicol • Erythromycin (macrolides • EXCEPT azithromycin) • Amiodarone • Omeprazole • Grapefruit juice • Quinidine

Chapter 2:
Drug Toxicity, Reversal & Side Effects

Drug Reactions and Causative Agents

Drug reaction	Causing drugs	Mnemonics
Teeth discoloration	• *Tetracyclines*	teethracyclines
Nephrotoxicity/ ototoxicity	• *Aminoglycosides*, Vancomycin, loop diuretics, Cisplatin, amphotericin B	
Photosensitivity	• Sulfonamides, Amiodarone, Tetracyclines, 5-FU	SAT For Photo
Hyperuricemia (gout)	• Pyrazinamide, Thiazides, Furosemide, Niacin, Cyclosporine	Painful Tophi and Feet Need Care
Osteoporosis	• Corticosteroids, depot medroxyprogesterone acetate, GnRH agonists, aromatase inhibitors,	
Gray baby syndrome	• *Chloramphenicol*	
Hemolysis in G6PD deficiency	• *Isoniazid, Sulfonamides, Dapsone, Primaquine, Aspirin, Ibuprofen, Nitrofurantoin*	Hemolysis IS D PAIN
Thrombocytopenia	• *Heparin*	
Megaloblastic anemia	• *Hydroxyurea, Phenytoin, Methotrexate, Sulfa drugs*	You're having a mega blast with PMS
Hepatitis	• *T.B drugs (Rifampin, Isoniazid, pyrazinamide)*	
Hepatic necrosis	• *Acetaminophen, Halothane, Valproic acid*	
Pancreatitis	• *Didanosine*, Corticosteroids, Alcohol, Valproic acid, Azathioprine, Diuretics (*furosemide, Hydrochlorothiazide)*	Drugs Causing A Violent Abdominal Distress
Pseudomembranous colitis	• *Clindamycin*, fluoroquinolones, Ampicillin, cephalosporins	
Diabetes insipidus	• Lithium, demeclocycline	
Dilated cardiomyopathy	• *Anthracyclines (e.g., doxorubicin, daunorubicin); prevent with dexrazoxane*	
Torsades de pointes	• AntiArrhythmics (class IA, III), antiBiotics (e.g., macrolides), anti"C"ychotics (e.g., haloperidol), antiDepressants (e.g., TCAs), antiEmetics (e.g., ondansetron)	ABCDE
Dry cough	• *ACE inhibitors*	

Toxicity and Treatments

Toxicity	Treatment
Acetaminophen	N-acetylcysteine (replenishes glutathione)
Organophosphates (AChE inhibitors)	Atropine > pralidoxime
Benzodiazepines	Flumazenil
Heparin	Protamine sulfate
Iron	Deferoxamine, Deferasirox, Deferiprone (3D'S)
OpiOids	NalOxOne
Warfarin	Vitamin K (delayed effect), fresh frozen plasma (immediate)
anticholinergic (atropine) toxicity	Physostigmine

Chapter 3: Autonomic Drugs

Effect of the Autonomic Nervous System on Organ Systems

- *Remember a rule, α1 is for constriction, α2 is for inhibition, β1 is for heart, β2 is for relaxation*

Organ	Sympathetic Action	Sympathetic Receptor	Parasympathetic Action	Parasympathetic Receptor
Heart	↑heart rate ↑contractility ↑AV node conduction	β1 β1 β1	↓ heart rate ↓contractility ↓AV node conduction	M2 M2 M2
Vascular smooth muscle	Constricts blood vessels in skin; splanchnic *Dilates blood vessels in skeletal muscle*	α1	---------- ----------	
Gastrointestinal tract	↓motility *Constricts sphincters*	α2, β2 α1	↑motility *Relaxes sphincters*	M3 M3
Bronchioles	*Dilates bronchiolar smooth muscle*	β2	*Constricts bronchiolar smooth muscle*	M3
Male sex organs	*Ejaculation*	α	*Erection*	M
Bladder	Relaxes bladder wall Constricts sphincter	β2 α1	Contracts bladder wall *Relaxes sphincter*	M3 M3
Sweat glands	↑sweating	M (sympathetic cholinergic)	----------	
Eye	*Dilates pupil (myDriasis)-- (far vision)*	α1	Constricts pupil (miosis)-- (near vision)	M
Kidney	↑renin secretion	β1	------------	
Fat cells	↑lipolysis	β1	------------	

Parasympathomimetics or Cholinomimetics

- *Stimulates the parasympathetic nervous system*

Drug	Action	Applications
Methacholine	Stimulates muscarinic receptors in airway when inhaled	Challenge test for diagnosis of asthma
Pilocarpine	Contracts ciliary muscle of eye (open-angle glaucoma), pupillary sphincter (closed-angle glaucoma);	*Open-angle and closed-angle glaucoma*
Galantamine, donepezil, rivastigmine	↑ Ach.	*Alzheimer disease*
Edrophonium	↑ Ach.	*Used to diagnose myasthenia gravis*
Physostigmine	↑ Ach.	*Antidote for anticholinergic toxicity (Atropine)*
Pyridostigmine	↑ Ach.	*Myasthenia gravis*

Parasympahtolytics or Anticholinergics

- Reduces the activity of the parasympathetic nervous system

Drugs	Organ Systems	Applications
Atropine	Eye	*Produce myDriasis (Dilates pupil)*
Hyoscyamine, dicyclomine	GI	Antispasmodics for irritable bowel syndrome
Ipratropium	Respiratory	*COPD, asthma*

Sympathomimetics

(↑ activity of sympathetic nervous system)

Drugs	Action	Applications
Epinephrine	$\beta > \alpha$	Anaphylaxis, asthma, open-angle glaucoma
Norepinephrine	$\alpha 1 > \alpha 2 > \beta 1$	Hypotension, septic shock
Dopamine	$D > \beta > \alpha$	Bradycardia, HF, shock • Low dose stimulates mainly dopaminergic receptors, producing renal and mesenteric vasodilation • higher dose stimulates both β1-adrenergic and dopaminergic receptors, producing cardiac stimulation and renal vasodilation • Large dose stimulates alpha-adrenergic receptor
Albuterol, Salmeterol.	$\beta 2 > \beta 1$	Albuterol for acute asthma or COPD Salmeterol for long-term asthma or COPD control
Amphetamine	Reuptake inhibitor	Narcolepsy, *ADHD* (attention deficit hyperactivity disorder)

Sympatholytics

(↓activity of sympathetic nervous system)

Drug	Action	Applications
Phenoxybenzamine	α blocker	Pheochromocytoma
Prazosin, tamsulosin	α1 selective	Urinary symptoms of BPH
α-methyldopa	α2-agonists	*Hypertension in pregnancy*

Chapter 4: Cardiovascular

Anti-Hypertensive Drugs

	Drug class	Drug name	Mechanism	Uses	Side effects
Diuretics	• Thiazide diuretics	Hydrochlorothiazide	Inhibits Na and Cl absorption. Inc Ca++ absorption *Thiazide Diuretics acts on early DT*	• CHF • Hypertension • Nephrosis • Diabetes insipidus • *Calcium calculi (as inc absorption so decreases Ca++ in urine)*	• Hyponatremia • *Hypokalemia* • *Hypercalcemia* • *↓clearence of lithum*
	• Loop diuretics Loops Lose Ca^{2+}.	Furosemide	*Inhibit cotransport system (Na+/K+/2 Cl-) of thick ascending limb of loop of Henle.*	• CHF • Hypertension • Hypercalcemia.	• Hyponatremia • *Hypokalemia* • ***Hypocalcemia*** • Ear- toxicity. deafness • *Dehydration*
	• K+ sparing diuretics The K+ STAys.	Spironolactone Epelerone Amiloride	Dec Na+ reabsorption and Dec K+ excretion *K+ sparing diuretics acts on collecting ducts*	Same as above	• ***Hyperkalemia*** • *Gynecomastia*
Drugs That Alter Sympathetic Nervous system	• Centrally acting sympa tholytic	Methyldopa	*inhibits adrenergic (sympathetic) system* Converted to methhy lnorepinephrine interacts with α-2 receptors→↓ sympathetic outflow Reduces renal vascular resistanceinc →urine output→Dec B.P	Hypertension *Safe in pregnancy*	• Dry mouth • Drowsiness • Hepatotoxicity • *Rebound hypertension*
	Adrenore ceptors blocker	Prazosin (α-blocker) *Propranolol ('-blocker)* *Labetalol (α-β-blocker)*			• *β-blockers (Propranolol) contraindicated in asthma β-blockers inhibits insulin*

Direct Acting Vasodilators		• Hydralazine	Relaxation of *smooth muscles of arteries and arterioles>> veins, so afterload reduction*	• Severe hypertension • *Safe in pregnancy* • Used with β-blocker to prevent reflex tachycardia	*Tachycardia* (contraindicated in angina/CAD)
Angiotensin Blockers	• Angiotensin converting enzyme inhibitors	• Captopril • Enalapril	Block peptidyl dipeptidase enzyme that converts angiotensin→ vasodilation *Inhibits bradykinin metabolism which is a vasodilator*	Hypertension *Diabetic nephropathy*	*Cough (due to bradykinin)* Hypotension
	• Angiotensin receptor blocker	• Losartan • Valsartan	Inhibits angiotensin 2 receptors	*Same as above*	No cough
Calcium Channel Blockers	DIHYDRO PYRIDINES	• Nifedipine • Amlodipine • Nimodopine	Block voltage gated L Ca++-channels→↓muscle contractility	• *CHF (only nimodopine→stroke and subarachanoid hemorrhage)* • Hypertension • angina	Cardiac depression AV block Constipation
	NON DIHYDROP YRIDINE	• Verapamil • Diltiazem	Same as above, BUT *dihydropyridine act on vascular smooth muscle while non-dihydropyridine on heart.* Dec SA and AV node activity	Same as above	*Peripheral edema (ankle edema)* Flushing Dizziness

Anti-Anginal Therapy

Drug class	Drugs	Mechanism	Uses	Side effects
Nitrates and nitrites	• Nitroglycerin • Isosorbide dinitrate • Isosorbide mononitrate.	Vasodilate by↑NO in vascular smooth muscle -- smooth muscle relaxation. Dilate veins >> arteries→↓preload	Angina ACS Pulmonary edema	• **Reflex tachycardia** (treat with β-blockers), • hypotension, • headache, • "Monday disease
β-blockers	• Propranolol		Angina	• Asthma • *(pindolol and acebutalol partial β agonists so contraindicated in angina)*
Ca++ channel blockers	already explained above		Angina	

Drugs Used In Heart Failure

Drug Class	Subclass	Drug Names	Mechanism	Uses	Side Effects
+I've inotropic agents	• Cardiac glycosides (digitalis)	• Digoxin • Digitoxin • Ouabin	• Direct inhibition of Na+/K+ ATPase →indirect inhibition of Na+/Ca2+ exchanger.↑ Ca2+→positive inotropy. Stimulates vagus nerve→ ↓HR.	CHF AV nodal tachycardia	• Cholinergic—nausea, vomiting, diarrhea, • blurry yellow vision (think van Gogh), • Arrhythmias, • AV block, • hyperkalemia
	• Bipyridines	• Amrinone	Inhibits phosphodiesterase enzymeinc→ cAMPinc→Ca++		
	• '-1 stimulant	• Dobutamine Dopamine	Vasodilation and positive inotropic effect by stimulating β-1 reoptors.	*Cardiogenic shock* *Dopamine cannot cross BBB*	
Diuretics		already explained			
Vasodilators	• ACE Inhibitors • Angiotensin receptor blocker • Direct vasodilators				

Antiarrhythmic Agents

Drug Class	Subclass	Drug	Mechanism	Uses	Side Effects
Class-I (Sodium channel blockers)	**Class IA**	• Quinidine, • Procainamide • Disopyramide The Queen Proclaims Diso's pyramid	Blocks Na channels →↓ Phase 0 depolarization	*Arrhythmias* *I-B is Best post-MI.* *I-C is proarythmatic so Contraindicated in structural and ischemic heart disease.* *Quinidine besides arrhythmias has also antimalarial property*	headache tinnitus with quinidine IC-Proarrhythmic
	Class IB	• Lidocaine			
	Class IC	• Flecainide • Propafenone. "Can I have Fries, Please"			

Drug Class	Subclass	Drug	Mechanism	Uses	Side Effects
Class-II *β- blockers*		• Metoprolol • Propranolol • Atenolol • Carvedilol	Decrease SA and AV nodal activity by → ↓slope of phase 4.	SVT, ventricular rate control for atrial fibrillation and atrial flutter	Exacerbation of COPD and asthma
Class-III *Potassium channel blockers*		• *Amiodarone* • Ibutilide • *Dofetilide* • Sotalol. AIDS.	Slow repolarization in phase III by K+ channel blockage	Atrial fibrillation, atrial flutter	*Amiodarone— pulmonary fibrosis, hepatotoxic, hypo or hyperthyroidism,* **Remember to check PFTs, LFTs, and TFTs** when using Amiodarone
Class-IV *Calcium channel blockers*		• Verapamil • Diltiazem.		SVT, rate control in atrial fibrillation	Constipation **Verapamil contraindicated in VT**

Beta-blockers overdose:

- Overdose of beta-blockers or calcium channel blocker can lead to significant bradycardia.
- If taken **within one hour** of presentation, **activated charcoal** should be tried.
- If there is symptomatic bradycardia **atropine** should be used **in the first instance.**
- **Glucagon** can be effective but this should be tried after atropine.

Pacing may be necessary if these drug treatments fail.

Chapter 5: Respiratory

Drug class	Sub class	Drug name	Mechanism	Uses	Side effects
Anti-histamines (H_1 blockers)	1st generation	• Diphenhydramin • Dimenhydrinate • Chlorpheniramine	Reversible inhibitors of H1 histamine receptors.	Allergy, motion sickness	*Sedation* antimuscarinic
	2nd generation	• Loratadine • Fexofenadine • Desloratadine • Cetirizine		Allergy	No or less sedation
Expectorants		• Guaifenesin		Expectorant	
		• N-acetylcysteine		Mucolytic Antidote for acetaminophen overdose	
		• Dextromethorphan	Antagonizes NMDA glutamate receptors	Antitussive.	*Naloxone can be given for overdose*
Alpha agonist		• Pseudoephedrine • Phenylephrine		Nasal decongestants	
Pulmonary hypertension drugs		• Bosentan.	Endhothelin receptor antagonists		
		• Sildenafil			
Asthma drugs	β2-agonists	• Albuterol • Salmeterol • Formoterol			
	Muscarinic antagonists	• Ipratropium	Competitively blocks muscarinic receptors, preventing bronchoconstriction. Also used for COPD.		
	Methylxanthines	• Theophylline	Bronchodilation inhibiting phosphodiesterase Metabolized by cytochrome P-450. Blocks actions of adenosine		Cardiotoxicity Neurotoxicity *Angina worsen by theophyline*

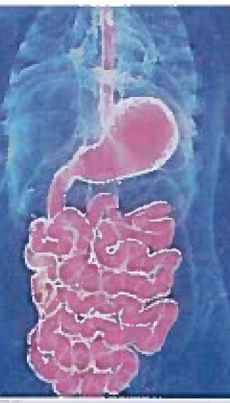
Chapter 6: Renal

Diuretics

Drug class	Drug name	Mechanism	Uses	Side effects
Carbonic anhydrase inhibitors	Acetazolamide	*Acts on PCT*	• Glaucoma	• renal tubular acidosis,
• Thiazide diuretics	Hydrochlorothiazide	Inhibits Na and Cl absorption. Inc Ca++ absorption *Thiazide Diuretics acts on early DT*	• CHF • Hypertension • Nephrosis • Diabetes Insipidus *Calcium calculi (as inc absorption so decreases Ca++ in urine)*	• Hyponatremia • *Hypokalemia* • *Hypercalcemia* • *↓clearence of lithum*
• Loop diuretics Loops Lose Ca2+.	Furosemide	*Inhibit cotransport system (Na+/K+/2 Cl-) of thick ascending limb of loop of Henle.*	• CHF • Hypertension • Hypercalcemia.	• Hyponatremia • *Hypokalemia* • ***Hypocalcemia*** Ear- toxicity. deafness • *Dehydration*
• K+ sparing diuretics The K+ **STA**ys.	Spironolactone Epelerone Amiloride	Dec Na+ reabsorption and Dec K+ excretion *K+ sparing diuretics acts on collecting ducts*	Same as above	• ***Hyperkalemia*** • *Gynecomastia*

Quick Summary

↓Na in blood (Hyponatremia)	All diuretics
↑ urine NaCl	All diuretics
↓K in blood (Hypokalemia)	Thiazide and loop diuretics
↑K in blood (Hyperkalemia)	K+ sparing diuretics
↑K in Urine	Thiazide and loop diuretics
↑Ca2+ in blood (Hypercalcemia)	Thiazide diuretics
↑Urine Ca2+	Loop diuretics (Loops Lose Ca2+)



Chapter 7: Gastrointestinal

Drug class	Drug name	Mechanism	Uses	Side effects
Proton pump inhibitors	Omeprazole Lansoprazole Esomeprazole Pantoprazole	• Irreversibly inhibit H+ /K+ ATPase in stomach parietal cells	• Peptic ulcer • gastritis • esophageal reflux Zollinger-Ellison syndrome	• *Increased risk of C. difficile infection* • Pneumonia
H2 blockers	Cimetidine Ranitidine Famotidine	• Reversible block of histamine H2-receptors →↓H+ secretion by parietal cells	• Same as above	• *Cimetidine is a potent inhibitor of cytochrome P-450 (multiple drug interactions)* • *it also has antiandrogenic effects (prolactin release, gynecomastia, impotence,↓libido in males)* • Can cross blood-brain barrier
Antacids	Bismuth, sucralfate	• Bind to ulcer base, providing physical protection and allowing HCO3– secretion to re-establish pH gradient in the mucous layer	• ↑ulcer healing Travelers' diarrhea.	
	Misoprostol	• PGE1 analog.↑ production and secretion of gastric mucous barrier ↓acid production	• Prevention of NSAID-induced peptic ulcers	• Diarrhea. Contraindicated in women of childbearing potential (abortifacient)
	Octreotide	• Long-acting somato statin analog • Inhibits actions of many splanchnic vasoconstriction hormones	• *Acute variceal bleeds* • acromegaly VIPoma • carcinoid tumors	• Nausea • Cramps • Steatorrhea

Metoclopramide	• D2 receptor antagonist. ↑ *Motility.* • Does not influence colon transport time	• Diabetic and post-surgery *gastroparesis* • Antiemetic	• Restlessness, drowsiness, fatigue, depression, *contraindicated in patients with small bowel obstruction or Parkinson disease (due to D1-receptor blockade).*
Ondansetron	• *5-HT3 antagonist* • *Powerful central-acting antiemetic*	• *Control vomiting postoperatively and in patients undergoing cancer chemotherapy.*	Headache, constipation QT interval prolongation *Serotonin syndrome.*

Chapter 8: Endocrinology

IV Anti-Diabetic (Insulin)

Insulin Type	Rapid Acting	Short Acting	Intermediate Acting	Long Acting
Examples	Lispro Aspart Glulisine	Regular	NPH	Detemir Glargine
Onset	< 15 minutes	30-60 mins	1-2 hours	1-2 hours
Duration of Action	3-6 hours	6-10 hours	10-18 hours	upto 24 hours

Oral Anti-diabetics

Class	Drug names	Mechanism of Action	Side Effects
Biguanides	Metformin	↓gluconeogenesis, ↑glycolysis, ↑glucose uptake (by ↑ insulin sensitivity).	GI upset Contraindicated in Renal insufficiency B12 deficiency anemia
Sulfonylureas	**1st generation:** Chlorpropamide Tolbutamide **2nd generation:** Glimepiride Glipizide Glyburide	Close K+ channel in β cell membrane→cell depolarizes→Insulin release via↑Ca2+ influx.	hypoglycemia Weight gain
Meglitinides	Nateglinide, Repaglinide	Stimulate postprandial insulin release by binding to K+ channels on β cell membranes (site differs from sulfonylureas).	
Thiazolidinediones	Pioglitazone Rosiglitazone	↑ insulin sensitivity in peripheral tissue Safe to use in renal impairment.	Weight gain, edema, HF, inc risk of fractures.
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	Sitagliptin Vildagliptin	Inhibit the degradation of the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).	
α-glucosidase inhibitors	Acarbose	Inhibit intestinal brush-border α-glucosidases. Delayed carbohydrate hydrolysis and glucose absorption→↓ after meal hyperglycemia	GI upset

GLP-1 analogs	Exenatide, liraglutide (sc injection)	Inc. glucose-dependent insulin release, Dec glucagon release, Dec gastric emptying, Inc. satiety	Nausea, vomiting, pancreatitis;

Anti-Hyperthyroidism

Drug names	Mechanism of Action	Uses	Side Effects
Propylthiouracil **Methimazole.**	Block thyroid peroxidase→ inhibition of thyroid hormone synthesis	• Hyperthyroidism. • *PTU used in first trimester of pregnancy (due to methimazole teratogenicity)* • *Methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity).*	Methimazole teratogen PTU hepatotoxicity Aplastic anemia

Hypothyroidism

Drug names	Mechanism of Action	Uses	Side Effects
Levothyroxine **Triiodothyronine**	Thyroid hormone replacement	Hypothyroidism	Tachycardia Heat intolerance

Lipid lowering agents

Drug	Mechanism of Action	Adverse effects
Statins	HMG CoA reductase inhibitors	**Myositis**, deranged LFTs
Ezetimibe	Decreases cholesterol absorption in the small intestine	Headache
Nicotinic acid	Decreases hepatic VLDL secretion	Flushing, myositis
Fibrates	Agonist of PPAR-alpha therefore increases lipoprotein lipase expression	Myositis, pruritus, **cholestasis**
Cholestyramine	Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid	GI side-effects

Chapter 9: Hematology and Oncology

Heparin and Warfarin

	Heparin	Warfarin
Route Of Administration	*Parenteral (IV, SC)*	*Oral*
Mechanism Of Action	*Activates antithrombin, which ↓ the action of IIa (thrombin) and factor Xa*	*Impairs synthesis of vitamin K-dependent clotting factors II, VII, IX, and X, and anticlotting proteins C and S*
Toxicity Treatment	*Protamine sulfate*	*Prothrombin complex concentrate PPC and FFP (for rapid reversal)* *Vitamin K,*
Monitoring	*PTT (intrinsic pathway)*	*INR > PT (↑PT (extrinsic pathway)*
Pregnancy	*can be given as it does not crosses placenta*	*shouldn't be given as it crosses placenta (teratogenic)*
Adverse effect	Heparin-induced thrombocytopenia (HIT) Bleeding	Early transient Hypercoagulability

Factor Xa Inhibitors, Thrombolytic, And Platelet Aggregation Inhibitors

Class	Drugs	Mechanism	Uses
Direct factor Xa inhibitors	*ApiXaban* *rivaroXaban*	*Bind to and directly inhibit factor Xa.*	Treatment and prophylaxis for DVT and PE
Thrombolytics	Alteplase (tPA), streptokinase.	Directly or indirectly aid conversion of plasminogen to plasmin, which cleaves thrombin and fibrin clots	Early ischemic stroke, Pulmonary Embolism Early MI
ADP receptors inhibitors	Clopidogrel, prasugrel, ticagrelor (reversible), ticlopidine	Inhibit platelet aggregation by irreversibly blocking ADP (P2Y12) receptor. Prevent expression of Glycoproteins IIb/IIIa on platelet surface.	Neutropenia (ticlopidine). TTP may be seen
Dipyridamole	Phosphodiesterase inhibitors; ↑cAMP in platelets, resulting in inhibition of platelet aggregation		

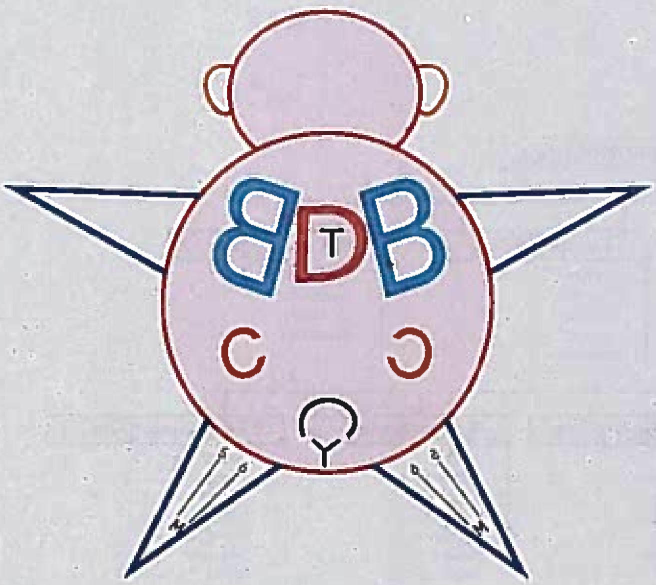
Glycoprotein IIb/IIIa inhibitors	Abciximab, eptifibatide, tirofiban.	Bind to the glycoprotein receptor IIb/IIIa on activated platelets, preventing aggregation	
Aspirin		*Irreversibly inhibits cyclooxygenase (both COX-1 and COX-inhibits the production of thromboxane A2*	

Cancer Drugs and Toxicity

Drugs Names	Site Of Action	Notes
MTX, 5-FU **6-MP (Mercaptopurine)** **Hydroxyurea**	Nucleotide synthesis inhibitors	Hydroxyurea→↓DNA Synthesis (S-phase specific).
Bleomycin **doxorubicin** **Etoposide**	DNA synthesis inhibitors	Etoposide inhibits topoisomerase II
Vincristine **Paclitaxel**	Inhibits cellular division	
Imatinib	Tyrosine kinase inhibitor	Used in CML, GI stromal tumors (GIST).
Tamoxifen	Estrogen receptor antagonists	Breast cancer treatment in Premenopausal
Anastrozole	Aromatase inhibitors	breast cancer in postmenopausal women

Toxicity

Chemotoxixity Man



Cisplatin and Carboplatin
- Ototoxicity

Nephrotoxicity

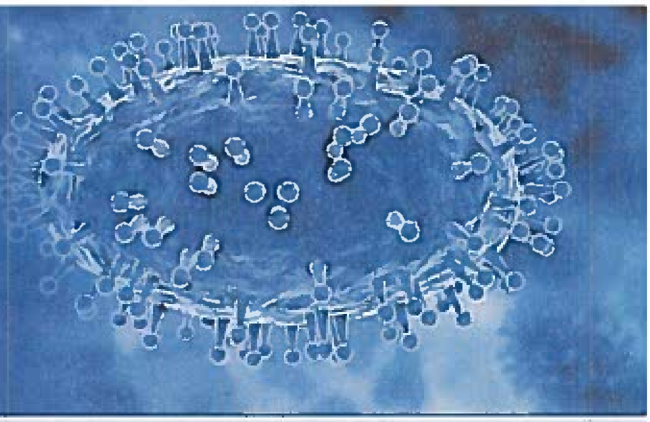
Vincristine
- Peripheral

Bleomycin, Busulfan
- Peripheral Neuropathy

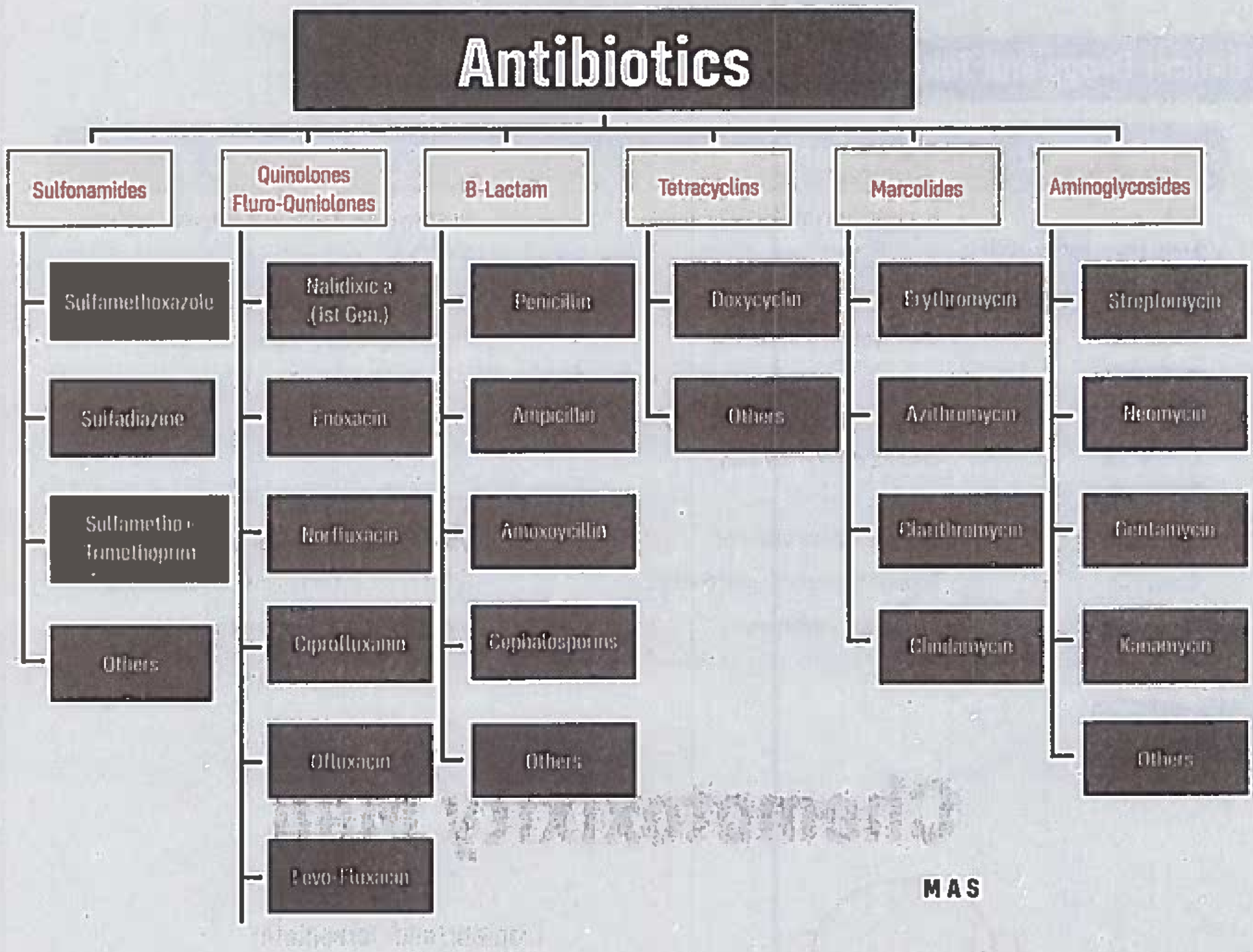
Trastuzumab and Doxorubicin
- Cardiotoxicity

Cyclophosphamide
- Hemorrhagic cytitis

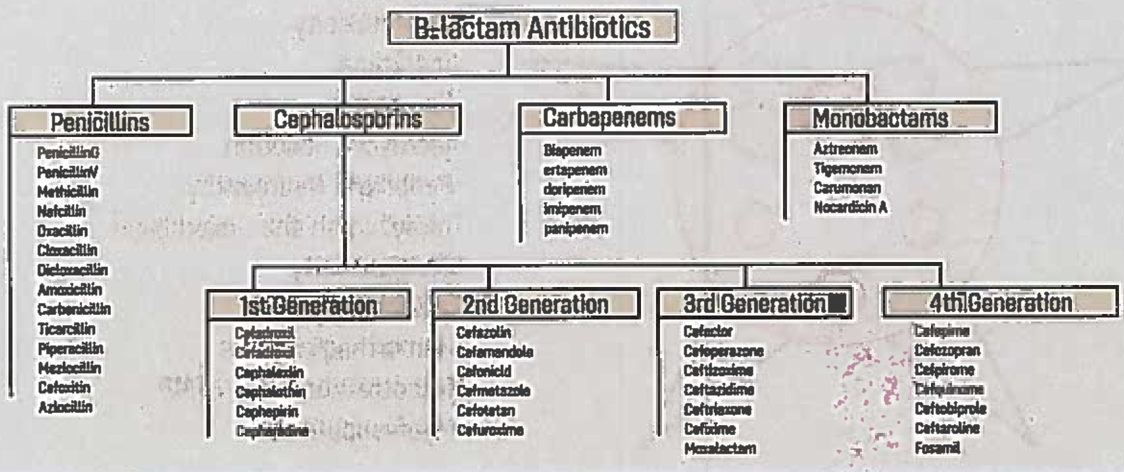
Methotrexate, 5-FU, 6-MP
- Myelosuppresion



Chapter 10: Antibiotics & Antivirals



MAS



Bactericidal antibiotics:

- B-lactam (Penicillin's, cephalosporin's), aminoglycosides, quinolones

Bacteriostatic antibiotics:

- Chloramphenicol, macrolides, Tetracyclines, sulfonamides

Mechanism of Action of Antibiotics

Mechanism of action	Examples	Notes
Interfering in bacterial cell wall synthesis	• Penicillin's	
	• Cephalosporins	• Organisms typically not covered by 1st–4th generation cephalosporins are **LAME: L**isteria, **A**typicals (Chlamydia, Mycoplasma), **M**RSA, and **E**nterococci.
	• Carbapenems (Imipenems, ertapenem, meropenem)	
	• Monobactams (aztreonam)	• Gram ⊖ rods only—no activity against gram ⊕ rods or anaerobes
	• Glycopeptide (Vancomycin)	• *Gram⊕ bugs only—serious, multidrug-resistant organisms, including MRSA*
Inhibiting protein synthesis through binding to 50S subunit of ribosome	• Chloramphenicol	• Adverse Effects: • *Aplastic anemia (dose independent)* • *Gray baby syndrome (in premature infants because they lack liver UDP- glucuronyltransferase).*
	• Macrolides (erythromycin, azithromycin)	• Adverse Effects: **MACRO** • Gastrointestinal **M**otility issues • **A**rrhythmia caused by prolonged QT interval • Acute **C**holestatic hepatitis, • **R**ash • e**O**sinophilia
	• Lincosamide (clindamycin, Lincomycin)	• *Treats anaerobic infections above the diaphragm with clindamycin, While metronidazole (anaerobic infections below Diaphragm)* • Adverse Effects:
Inhibiting protein synthesis through binding to 30S subunit of ribosome	• Aminoglycosides (streptomycin, gentamicin, Amikacin, neomycin)	• Severe gram ⊖ rod infections, Synergistic with β-lactam antibiotics. *Neomycin for bowel surgery.* Adverse Effects • *Nephrotoxicity, Ototoxicity (especially when used with loop diuretics) Teratogen*
	• Tetracyclines (oxytetracycline, methacyclin, doxycycline)	• Adverse Effects • *Discoloration of teeth and inhibition of bone growth in children, photosensitivity*
Inhibiting DNA synthesis	• Fluoroquinolones (ciprofloxacin, Norfloxacin, levofloxacin, ofloxacin)	

Inhibiting RNA synthesis	• Rifampin	
Inhibiting dihydrofolate reductase activity	• Sulfonamides, trimethoprim Dapsone	• Adverse effects: • *Hemolysis if G6PD deficient, nephrotoxicity* (tubulointerstitial nephritis), photosensitivity, *Stevens-Johnson syndrome*, kernicterus in infants • *Dapsone for Leprosy*
Disrupting bacterial membrane	• Polymyxin (Polymyxin B, Polymyxin E	
Inhibits bacterial protein synthesis by stopping 70s initiation complex	• Linezolid	• Highly active against gram positive organism including • MRSA, VRE (vancomycin resistant enterococcus), GISA (glycopeptide intermediate staph. Aureus) • Adverse effects→Thrombocytopenia (reversal

Antimicrobials to Avoid In Pregnancy

Antimicrobial	Adverse Effect
Sulfonamides	Kernicterus
Aminoglycosides	Ototoxicity
Fluoroquinolones	Cartilage damage
Clarithromycin	Embryotoxic
Tetracyclines	Discolored teeth, inhibition of bone growth
Ribavirin	Teratogenic
Griseofulvin	Teratogenic
Chloramphenicol	Gray baby syndrome
Mnemonic: **SAF**e **C**hildren **T**ake **R**eally **G**ood **C**are.	

Anti-HIV Agents

Nucleoside reverse transcriptase inhibitors "NRTI" (--INE in the end mostly)	Zidovudine Didanosine Lamivudine Stavudine	• *Zidovudine= Bone marrow suppression* • *Didanosine= Pancreatitis* • *Stavudine = Pancreatitis* • *Generally whole class GI intolerance & Lipoatrophy & peripheral neuropathy*
Non- Nucleoside reverse transcriptase inhibitors NNRTI"	Efavirenz Nevirapine	• Rash, hepatitis **Contraindicated in pregnancy**

Protease inhibitors "PI" (--VIR in the end mostly)	Ritonavir
	Indinavir
	Nelfinavir
		• Whole class
		  • GI intolerance
		  • TYPE 2 DM
		  • truncal obesity
		• ***Indinavir = Renal stones***

Anti-Viral treatment

Drugs	Mechanism	Uses	Side effects
Oseltamivir, zanamivir	Inhibit influenza neuraminidase	Influenza A and B. Beginning therapy within 48 hours of symptom onset may shorten duration of illness	• GI symptoms
Acyclovir, famciclovir, valacyclovir	Guanosine analogs inhibit viral DNA polymerase	HSV VZV	• Obstructive crystalline nephropathy and acute renal failure if not adequately hydrated
Ganciclovir	Guanosine analogs inhibit viral DNA polymerase	CMV	• Myelosuppresion
Foscarnet	pyrofosphate analog inhibit viral DNA polymerase	CMV retinitis in immunocompromised patients when ganciclovir fails Acyclovir-resistant HSV	• Nephrotoxicity • Electrolyte abnormalities (hypocalcemia, hypokalemia, hypomagnesemia) can lead to seizures
Amantadine	Inhibits un-coating of virus in cells	Influenza, Confusion , Parkinson's	• **Ataxia**

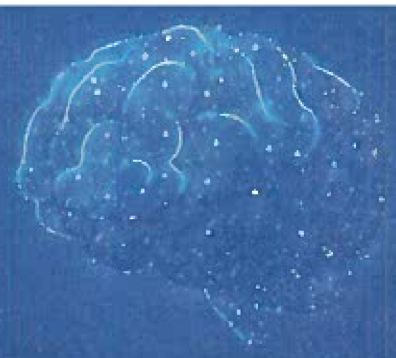
Hepatitis therapy

Drugs	Mechanism	Uses	Side effects
Ribavirin	Guanosine analogue inhibits inosine monophosphate (IMP) interferes with the capping of viral mRNA	Chronic HEP-C RSV	Hemolytic anemia Teratogen
Sofosbuvir	Inhibits HCV RNA-polymerase	Chronic HEP-C	
Simeprevir	HCV protease inhibitor	Chronic HEP-C	

Anti-TB drugs

Isoniazid	Inhibits mycolic acid synthesis	*Peripheral neuropathy, hepatitis*	*For prevention use pyridoxine*
Rifampicin	Inhibits RNA polymerase preventing transcription of DNA into mRNA	*Peripheral neuropathy, hepatitis*	*Does not need treatment*
Ethambutol	Inhibits arabinosyl transferase which polymerizes arabinose into arabinan	*Optic neuritis (color blindness)*	*Reduce dose or stop* ***Dose needs adjusting in renal impairment too***
Pyrazinamide	Inhibits fatty acid synthase	*Hepatitis Photosensitization, Hyperuricemia, gout*	*Contraindicated in pregnancy*
Streptomycin	Interferes with 30S component of ribosome.	*Vestibular (8th) nerve damage*	*Used only if patient has multi-drug resistant*

Chapter 11: Neurology



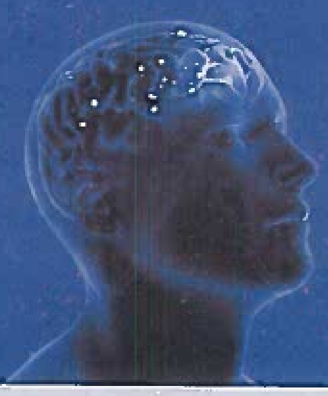
Antiepileptic drugs

Epilepsy type	Preferred 1st line Agent	Other 1st line agent	
Partial seizures	Carbamazepine (Phenobarbital in neonates)	Lamotrigine Sodium valproate	
Tonic clonic seizure	*Sodium valproate*	Lamotrigine	
Absence seizures	*Ethosuximide*	Sodium valproate	Carbamazepine may exacerbate
Myoclonic seizures	*Sodium valproate*	Clonazepam	
Status epilepticus	*benzodiazipines(e.g.diazepam)*		

Antiepileptic drugs

Drug name	Mechanism	Side effects	Used for
Ethosuximide	Blocks thalamic T-type Ca2+ channels	**EFGHI—** • **E**thosuximide causes Fatigue, **GI** distress, **H**eadache, **I**tching (and urticaria).	*Sucks to have Silent (absence) Seizures*
Benzodiazepines (eg. diazepam, lorazepam, midazolam)	↑GABAA action	• Sedation, tolerance, dependence • Respiratory depression	*Also for eclampsia seizures (1st line is MgSO4)*
Phenobarbital	↑GABAA action	• Sedation, tolerance, dependence, • Induction of cytochrome P-450 • Cardiorespiratory depression	*1st line in neonates*
Phenytoin, fosphenytoin	Blocks Na+ channels Follow zero-order kinetics	• Neurologic: Nystagmus, diplopia, ataxia, sedation, peripheral neuropathy. • Gingival hyperplasia • DRESS syndrome. • Musculoskeletal: SLE-like syndrome. • Hematologic: megaloblastic anemia. • Other: cytochrome P-450 induction	

Drug name	Mechanism	Side effects	Used for
Carbamazepine	Blocks Na+ channels	• Blood dyscrasias (agranulocytosis, aplastic anemia) Liver toxicity, teratogenesis, SIADH Stevens-Johnson syndrome	*1st line for trigeminal neuralgia*
Valproic acid	↑Na+ channel inactivation, ↑GABA concentration by inhibiting GABA transaminase	• GI distress • *Rare but fatal hepatotoxicity (measure LFTs).* • *Pancreatitis* • *Neural tube defects* • *Contraindicated in pregnancy*	Also used for myoclonic seizures, bipolar disorder, migraine prophylaxis



Chapter 12: Psychiatry

Class	Drugs	Mechanism	Clinical Use	Clinical Use
Lithium		• Not established; possibly related to inhibition of phosphoinositol cascade.	• Mood stabilizer for bipolar disorder • Blocks relapse and acute manic events.	LITHIUM: • *Low Thyroid (hypothyroidism)* • *Heart (Ebstein anomaly)* • *Insipidus (nephrogenic diabetes insipidus)* • *Unwanted Movements (tremor)*
Buspirone		• Stimulates 5-HT1A receptors.	• Anxiety disorders • Does not cause sedation, addiction, or tolerance.	
Selective serotonin reuptake inhibitors	• Fluoxetine • Paroxetine • Sertraline. • Escitalopram • Citalopram	• Inhibit 5-HT reuptake	• Depression, generalized anxiety disorder • premature ejaculation	• GI distress • SIADH
Serotonin norepinephrine reuptake inhibitors	• Venlafaxine • Desvenlafaxine • Duloxetine	• Inhibit 5-HT and norepinephrine reuptake	• Depression • General anxiety disorder • Diabetic neuropathy • **Duloxetine is also indicated for fibromyalgia.**	
Tricyclic antidepressants	• Amitriptyline • Nortriptyline • Imipramine • Desipramine • Clomipramine • Doxepin • Amoxapine	• Inhibit NE and 5-HT reuptake.	• Major depression • Peripheral neuropathy • Migraine prophylaxis • Nocturnal enuresis (imipramine)	• **Postural hypotension** • **Atropine-like (anticholinergic) side effects** (tachycardia, urinary retention, dry mouth). • **Can prolong QT interval** • **Management: IV bicarbonate**

Monoamine oxidase inhibitors (**MAO T**akes **P**ride **I**n **S**hanghai).	• **T**ranylcypromine • **P**henelzine • **I**socarboxazid, • **S**elegiline (selective **MAO**-B inhibitor).	• Nonselective MAO inhibition↑ **levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine).**	• Atypical depression • Anxiety • Parkinson disease (Selegiline).	• CNS stimulation • **Hypertensive crisis, most notably with ingestion of tyramine,** which is found in many foods such as aged cheese and wine. . • **Contraindicated with SSRIs, TCAs, St. John's wort,** meperidine, dextromethorphan **(to prevent serotonin syndrome)**

Serotonin syndrome

- Can occur with any drug that ↑ 5-HT (e.g., MAOIs, SSRIs, SNRIs, TCAs, tramadol, ondansetron, triptans, linezolid, MDMA, dextromethorphan).
- Characterized by **3 A's**: neuromuscular hyper**A**ctivity (clonus, hyperreflexia, hypertonia, tremor, seizure), **A**utonomic stimulation (hyperthermia, diaphoresis, diarrhea), and **A**gitation.
  Treatment: **cyproheptadine** (5-HT2 receptor antagonist).

Chapter 13: Musculoskeletal, Skin, and Connective Tissue

Gout drugs

Drug	Mechanism of action	Notes
Allopurinol	• Inhibitor of xanthine oxidase.	• ↑effect of Azathioprine, Cyclophosphamide & warfarin Side effects: Allopurinol Hypersensitivity Syndrome (AHS)
Febuxostat	• Inhibits xanthine oxidase	
Probenecid	• Inhibits reabsorption of uric acid in proximal convoluted tubule (also inhibits secretion of penicillin).	• Can precipitate uric acid calculi.
Colchicine	• Binds and stabilizes tubulin to inhibit microtubule polymerization, impairing neutrophil chemotaxis and degranulation.	• Acute and prophylactic value

Analgesics, NSAIDS, other drugs

Acetaminophen		• Reversibly inhibits cyclooxygenase	• Overdose produces hepatic necrosis • Acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. • **N-acetylcysteine is antidote—regenerates glutathione.**
Aspirin		• *Irreversibly inhibits cyclooxygenase (both COX-1 and COX-2)*	• Low dose (< 300 mg/day):↓platelet aggregation. • Intermediate dose (300–2400 mg/day): antipyretic and analgesic. • High dose (2400–4000 mg/day): anti-inflammatory. • Adverse effects: • Tinnitus, Gastric ulceration, interstitial nephritis, GI bleeding. Reye syndrome
Celecoxib		• Reversibly and selectively inhibits the cyclooxygenase (COX) 2	• Spares COX-1, which helps maintain gastric mucosa • Adverse effects: **INC. risk of thrombosis**
NSAIDS	• Ibuprofen • Naproxen • Indomethacin • Ketorolac • Diclofenac • Meloxicam • piroxicam	• Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). • Block prostaglandin synthesis	Adverse effects: • Interstitial nephritis • Gastric ulcer (prostaglandins protect gastric mucosa) • Renal ischemia (prostaglandins vasodilate afferent arteriole) • **Aplastic anemia.**

Bisphosphonates	• Alendronate • Ibandronate • Risedronate • zoledronate	• Pyrophosphate analogs; bind hydroxyapatite in bone, inhibiting osteoclast activity.	• Esophagitis (If taken orally, patients are advised to take with water and remain upright for 30 minutes) • Osteonecrosis of jaw • Atypical stress fractures

Allopurinol

Initiating allopurinol prophylaxis	• Allopurinol should not be started until 2 weeks after an acute attack has settled
Indications for allopurinol	• Recurrent attacks • Tophi, renal disease, uric acid renal stones, prophylaxis if on cytotoxics or diuretics • **Patients with Lesch-Nyhan syndrome often take allopurinol for life**

Allopurinol Hypersensitivity Syndrome (AHS)	• Recurrent attacks
	• Tophi, renal disease, uric acid renal stones, prophylaxis if on cytotoxics or diuretics
	Patients with Lesch-Nyhan syndrome often take allopurinol for life
	  ◦ **2%** of patients on allopurinol develop itchy maculopapular rashes
	  ◦ **5-10%** develop gastrointestinal dysfunction, and deranged liver function tests (LFTs)
	  ◦ **20%** of patients on allopurinol, who are prescribed amoxicillin or ampicillin develop a rash.

Paracetamol overdose

Risk factors	The following groups of patients are at an increased risk of developing hepatotoxicity following a paracetamol overdose: • Patients taking **liver enzyme-inducing drugs:** ◦ Rifampicin, phenytoin, carbamazepine, chronic alcohol excess, St John's Wort • **Malnourished patients** Patients **who have not eaten** for a few days A dose of > **150 mg/kg** is considered to be toxic
Management	All patients are treated the same regardless of risk factors for hepatotoxicity. • Check **paracetamol level four hours after** ingestion • Check **INR 12 hourly.** • **Gastric lavage** if large dose ingested **(more than 7.5 g)** and/or presenting within eight hours of ingestion. • Give **N-acetylcysteine or methionine.** **N-acetylcysteine should be given if** • There is a staggered overdose or • there is doubt over the time of paracetamol ingestion, regardless of the plasma paracetamol concentration; or **How to give Acetylcysteine** • Acetylcysteine is now **infused over 1 hour** (rather than the previous 15 minutes) to reduce the number of adverse effects.

Liver transplantation criteria "Kings college"	• Arterial **pH < 7.3**, 24 hours after ingestion **or all of the following:**
	  ◦ PT > 100 seconds **(Best indicator of prognosis)**
	  ◦ creatinine > 300 umol/l
	  ◦ Grade III or IV encephalopathy

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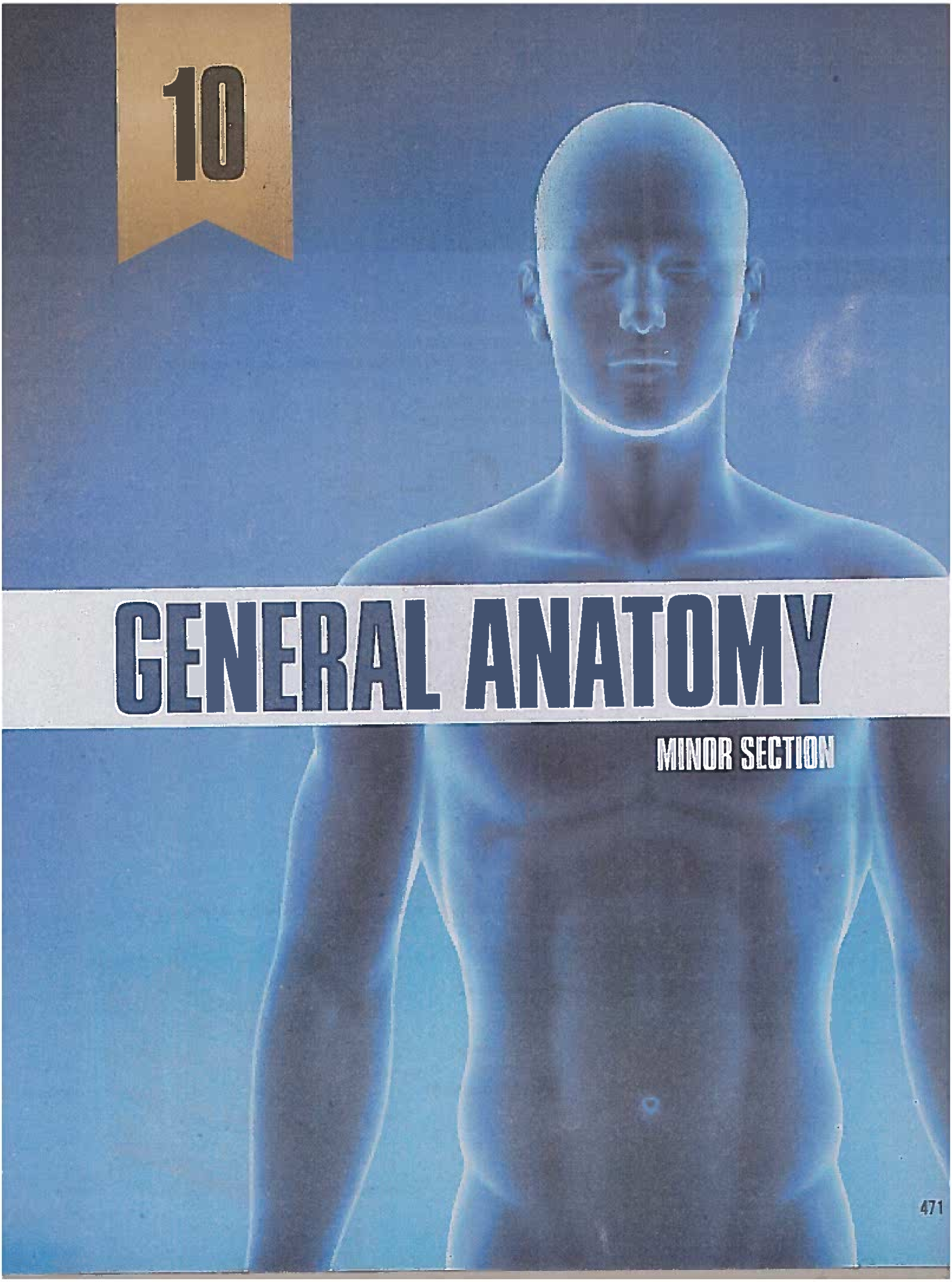


10

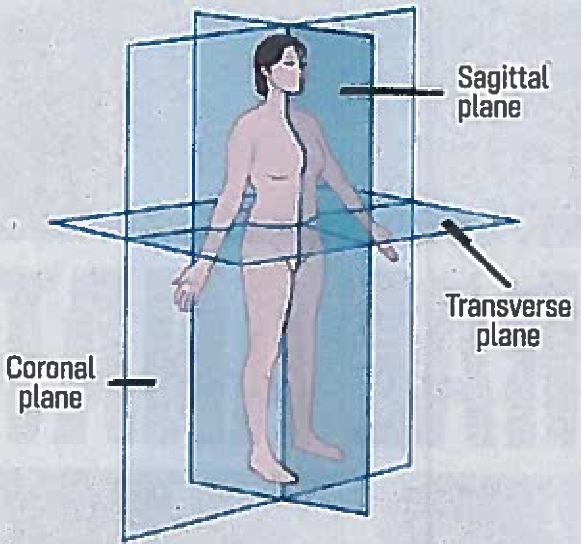
GENERAL ANATOMY

MINOR SECTION

Chapter :
General Anatomy

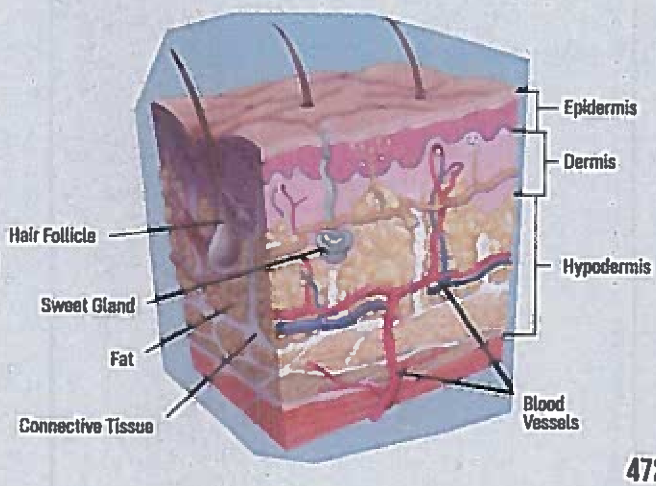
Anatomical planes

- Sagittal plane → it divides the body into left and right portions.
- Coronal plane→ it divides the body into anterior and posterior portions
- Transverse plane (also called the horizontal plane, axial plane) it divides the body into superior and inferior parts.
- Remember:
  - Flexion and extension takes place in sagittal section
  - Adduction and abduction take place in coronal section



Skin

- Largest organ of the body
- Skin has three layers:
  - The epidermis →the outermost layer of skin, provides a waterproof barrier
  - The dermis→beneath the epidermis, contains tough connective tissue, hair follicles, and sweat glands.
  - Hypodermis →The deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue.
- Melanocytes are located in the epidermis.
- Appendages of skin are nails, hair follicles, sebaceous and sweat glands.
- Layers of epidermis: **C**ome **L**et's **G**et **S**un **B**urned)
  - **C**orneum, **L**ucidum, **G**ranulosum, **S**pinosum, **B**asale
  - Location of Melanocytes in the skin: Stratum basalis (the deepest layer of the five Epidermis layers)

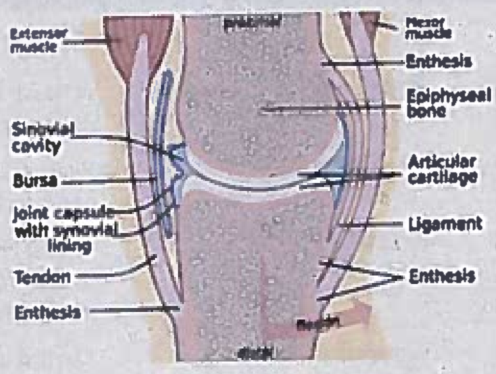


Skin Appendages

Hair follicles	• Invaginations of epidermis into the dermis. • Arrector pili are the bands of smooth muscles that connect the under surface of hair follicle to the superficial part of dermis. • It causes contraction of sebaceous gland and its secretion • Dimpling of skin called gooseflesh is due to the pull of the Arrector pili muscle.
Sebaceous glands	• Lie within the dermis and pour their secretion, the sebum ONTO the shaft of hairs. • Sebaceous glands are not present in lips, palms, sides of fingers, glans penis and clitoris, labia minora and internal surfaces of labia majora, soles, sides of feet and sides of toes. • Sebaceous cyst most frequently occurs at scalp. • Boil is infection of hair follicle and sebaceous gland. • Carbuncle is staphylococcal infection of superficial fascia.
Sweat glands	• Expand full thickness of dermis and their extremity may lie in superficial fascia. • They are the most deeply placed structure of all appendages. • Sweat glands are not present on red margins of lips, nail buds, glans penis, and clitoris
Burns	• Partial thickness burn heals from the cells of hair follicles, sebaceous and sweat glands and from the cells of edges of burn. • A burn that extends deeper than sweat gland heals slowly and only from edges
Nerve fibers	• Preganglionic are myelinated and type B fibers. • Postganglionic are non-myelinated and type C fibers
HILTON's LAW	• Sensory Nerve supplying the joint also supplies the muscles that cause movement on that joint and the skin overlying the insertion of these muscles

Bursa:

- Bursa is a small fluid-filled sac lined by synovial membrane with an inner capillary layer of viscous synovial fluid (similar in consistency to that of a raw egg white).
- It provides a cushion between bones and tendons and/or muscles around a joint.

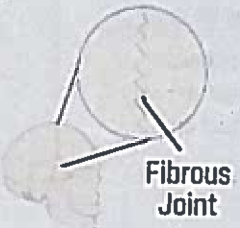


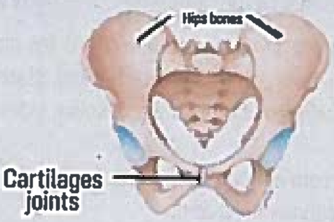
Joints:

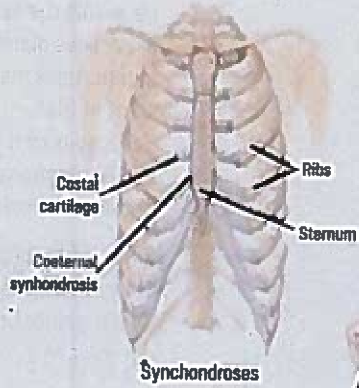
- Fusion of two bones is called joint.
- Types of joints

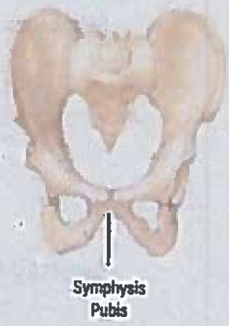
Joint type		Definition	Example
Fibrous Joints		The articulating surfaces of the bones are joined by fibrous tissue and thus very little movement is possible	Skull suture, inferior tibiofibular joints.
Cartilaginous Joints	Primary cartilaginous joint	Bones are united by a plate or a bar of hyaline cartilage. No movement is possible	Joint b/w epiphysis and the diaphysis. Joint b/w 1st rib and the manubrium sterni
	Secondary cartilaginous joint	Bones are united by a plate of fibrocartilage and the articular surfaces of the bones are covered by a thin layer of hyaline cartilage	Joints between the vertebral bodies and symphysis pubis

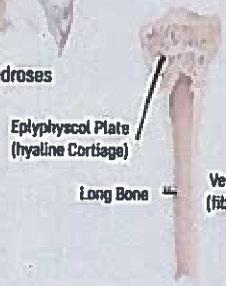
Synovial Joints	The articular surfaces of the bones are covered by a thin layer of hyaline cartilage separated by a joint cavity The cavity of the joint is lined by synovial membrane	

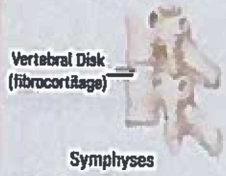








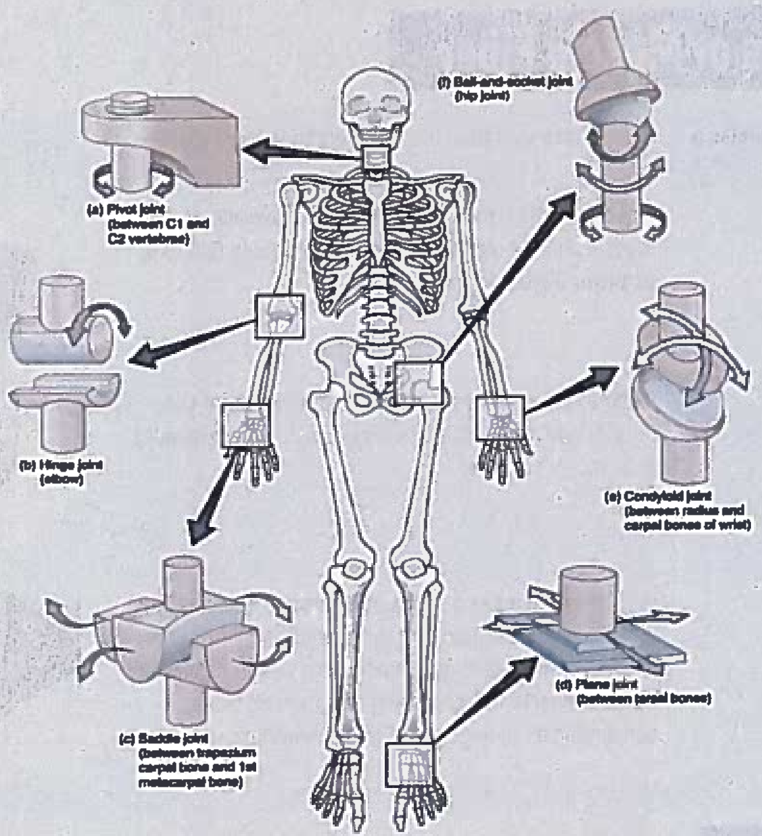




Types of synovial joints

Joint type	Definition	Example
Plane joints	Articular surfaces are flat. And this permits the bones to slide on one another.	Sternoclavicular & Acromioclavicular joints
Hinge joints	Hinge joints resemble the hinge on a door, so that flexion and extension movements are possible.	Elbow, knee, and ankle joints
Pivot joints	In pivot joints, a central bony pivot is surrounded by a bony ligamentous ring. Rotation is the only movement possible.	Atlantoaxial and superior radioulnar joints
Condyloid joints	Two distinct convex surfaces that articulate with two concave surfaces	Metacarpophalangeal joints or knuckle joints
Ellipsoid joints	Elliptical convex articular surface fits into an elliptical concave articular surface The movements of flexion, extension, abduction, and adduction can take place, but rotation is impossible	Wrist joint
Saddle joints	Articular surfaces are reciprocally concavo-convex and resemble a saddle on a horse's back These joints permit flexion, extension, abduction, adduction, and rotation.	Carpometacarpal joint of the thumb
Ball-and-socket joints	Ball- shaped head of one bone fits into a socket like concavity of another. This arrangement permits free movements, including flexion, extension, abduction, adduction, medial rotation, lateral rotation, and circumduction.	Shoulder and hip joints

(a) Pivot joint
(between C1 and
C2 vertebrae)



Muscles:

- Contractile tissue of body which brings about movements.

Types of Muscles

Striated muscle:	Unstriated muscle:
Skeletal muscle (voluntary) Cardiac muscle (involuntary)	Smooth muscle (involuntary) present in viscera.

Comparison OF Skeletal, Smooth And Cardiac Muscle

Skeletal muscle	Cardiac muscle	Smooth muscle
Striated	Striated	Non-striated
Voluntary	Involuntary	Involuntary
No intercalated disc	Intercalated disc present and a characteristic feature.	No intercalated disc
Very rapid contractions	Rapid contractions	Slow contractions
Multinucleated	Uninucleated	Uninucleated
Examples: • Limbs • Body wall • Tongue • Pharynx • Beginning of esophagus	Examples: • Wall of heart	Examples: • Distal part of esophagus • Urogenital tract • Urinary bladder • Blood vessels

Types of Muscle Fiber

Slow Fibers (Type 1)	Fast Fibers (Type 2)
Slow twitch	Fast twitch
Red fibers → because of large amounts of myoglobin	White fibers → because of small amounts of myoglobin
Rich in mitochondria	Decreased mitochondria

Arrangements of Muscle Fiber

Pennate muscles (resembles a feather)	Muscles whose fibers run obliquely to the line of pull	
Unipennate muscle	Muscle in which the tendon lies along one side of the muscle and the muscle fibers pass obliquely to it (e.g., extensor digitorum longus)	 unipenate
Bipennate muscle	Muscle in which the tendon lies in the center of the muscle and the muscle fibers pass to it from two sides (e.g., rectus femoris).	 biprnnate
Multipennate muscle	may be arranged as a series of bipennate muscles lying alongside one another (e.g., acromial fibers of the deltoid) or may have the tendon lying within its center and the muscle fibers passing to it from all sides, converging as they go (e.g., Tibialis anterior)	 multipennate

Blood Vessels:

- Blood vessels are of three types: arteries, veins, and capillaries

Arteries	• Transport blood from the heart • The smallest arteries, <0.1 mm in diameter, are referred to as arterioles • Arteries do not have valves • Anatomic end arteries are vessels whose terminal branches do not anastomose with branches of arteries • Joining of branches of arteries is called an anastomosis
Veins	• Veins are vessels that transport blood back to the heart • Many of them possess valves • The smallest veins are called Venules • Medium-size deep arteries are often accompanied by two veins, one on each side, called venae comitantes.
Capillaries	• Capillaries are microscopic vessels in the form of a network connecting the arterioles to the venules • Site of gas exchange

Bones

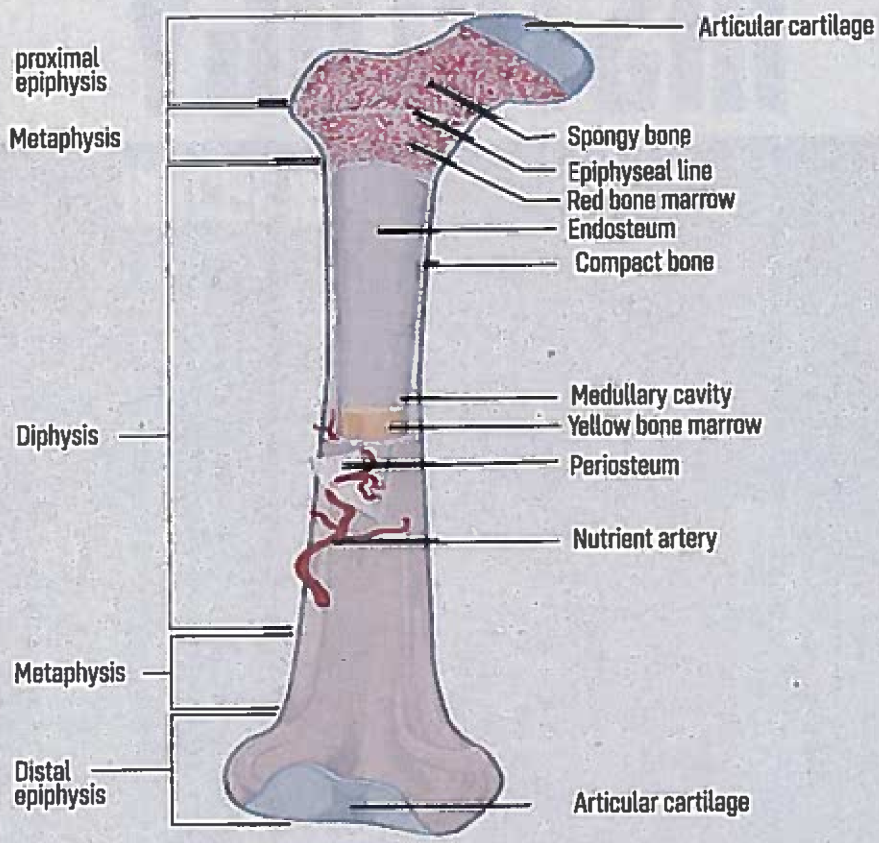
- At birth→ around 300 bones
- At adulthood → 206 bones.

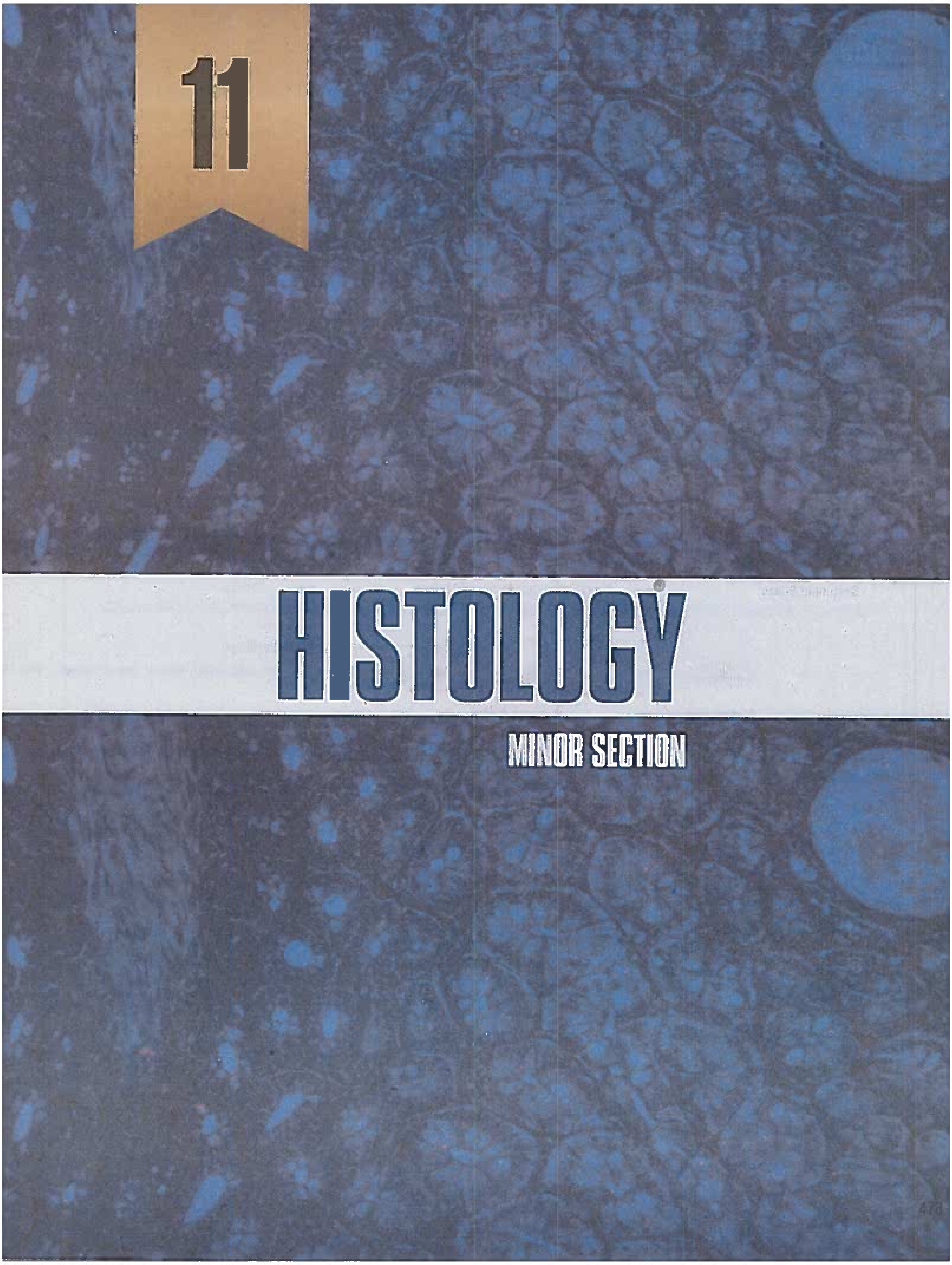
Classification of bones

Bone type	Description	Example

Long bone	• Length > diameter
	• The shaft has a central marrow cavity containing bone marrow.
	• The outer part of the shaft is covered by a connective tissue sheath, the periosteum.
	• In young long bone following parts can be identified:
	  • Epiphysis: the ends and the tips of a long bone that ossify from secondary centers are known as epiphyses
	  • Diaphysis term used for elongated shaft of the long bone. It ossifies from a primary center.
	  • Metaphysis the ends of diaphysis near the epiphyses are known as metaphysis
		• (humerus, ulna, radius) femur, tibia, fibula

Short bones	• Length = diameter/ width	• Carpal bones • Tarsal bones
Flat bones	• Thin bone, provides protection to soft tissues	• Cranial bones • Sternum • Ribs
Irregular bones	• Complicated shape, that cannot be classifies as short, long or flat bones	• Vertebrae's
Sesamoid Bones	• Round bone that forms in tendons	• Patella





11

HISTOLOGY

MINOR SECTION

Chapter: Histology

Epithelium

- Closely packed cells that covers body surfaces, cavities and tubes
- Types

Simple epithelium	Stratified epithelium
Consist of single layer of cells	Consist of two or more layers

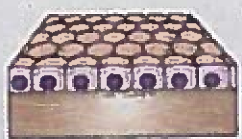
Further subtypes:
• Simple squamous (flat cells)
  • Examples: heart, blood vessels, alveoli
	Further subtypes:
	• Stratified squamous
	  • Keratinized →contains keratin
	    • Example: skin, parts of oral cavity
	  • Non-keratinized →no keratin
	    • Example: esophagus, oropharynx, lower part of anal canal, vagina

• Simple cuboidal (cube-like cells)
  • Examples: DCT of nephron, ovary
	• Stratified cuboidal
	  • Example: sweat gland ducts

• Simple columnar (column like cells)
  • Examples:
  • Non-Ciliated: stomach, gall bladder and intestine
  • Ciliated: uterine tubes, uterus
	• Stratified columnar
	  • Example: salivary glands ducts, male urethra

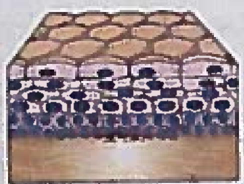
• Pseudostratified (single layer of cells but gives a false impression of stratification)
  • Examples: nasal cavity, nasopharynx, conducting part of respiratory tract.
	• Transitional epithelium
	  • Example: renal pelvis, ureter, urinary bladder, part of urethra.


simple squamous


simple cuboidal


Simple columnar with microvilli


Stratified squamous


Transitional


Pseudostratified columnar with cillia and microvilli

Bronchioles Epithelium

Primary bronchioles/ Preterminal	Simple ciliated columnar to simple cuboidal
Respiratory bronchioles	Simple cuboidal except where interrupted by alveoli
Alveolar ducts and alveoli	Simple squamous

Collagen

- Most abundant protein in body
- Organizes and strengthens extracellular matrix.
- Types of collagen

Type	Examples	Notes
Type-I	Bone, Skin, Tendon, fascia, late wound healing	• Most abundant form (90%) • ↓ Production in osteogenesis imperfecta type I.
Type- II	Cartilage (including hyaline), vitreous body and nucleus pulposus.	
Type- III	Reticular fibers. granulation tissue, embryonic tissue, uterus, blood vessels, early wound healing	• Type III: deficient in the vascular type of Ehlers-Danlos syndrome
Type- IV	Basement membrane, basal lamina, lens	• Defective in Alport syndrome • Targeted by autoantibodies in Goodpasture syndrome

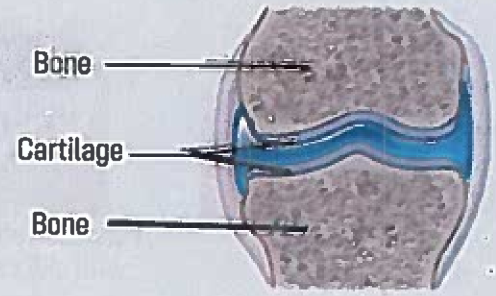
Note How to remember it:
The higher number you go the weaker it goes

- Type I is the strongest as it is located in bones, skin, tendons, fascia
- Type II little bit less strength seen in cartilage, vitreous humor, and nucleus pulposus
- Type III goes even weaker as it is present in granulation tissue, embryonic tissue, uterus, blood vessels
- Type IV is the weakest is it only supports a row of epithelial cells as it's found only in basement membranes

Another mnemonic:
Type **ONE= BONE**, type **TWO=** car**TWO**lage, type **FOUR= FLOOR** (**BASEMENT** membrane)

Cartilage

- Cartilage is a resilient and smooth elastic tissue, rubber-like padding that covers and protects the ends of long bones at the joints.
- Structural component of the rib cage, the ear, the nose, the bronchial tubes, the intervertebral discs, and many other body components.
- Types:



Hyaline cartilage	Fibro-cartilage	Elastic cartilage
Called hyaline (glass like), because fibers are not visible	Fibers are visible	Fibers are visible
Composed of collagen type II	Composed of collagen type I	Collagen type II
Examples (ENT CAAR) • Epiphyseal cartilage of growing long bones • Nasal cartilage • Thyroid cartilage • Cricoid cartilage • Articular cartilage • Arytenoid cartilage • Ribs (costal cartilage)	Examples • Intervertebral discs • Glenoid labrum • Acetabular labrum • Menisci of knee	Examples Elastic cartilage→3E • Ear pinna • External auditory tube • Epiglottis

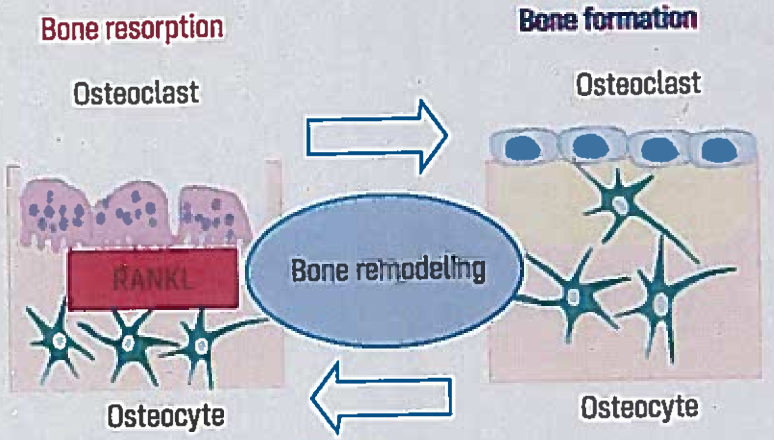
Bone

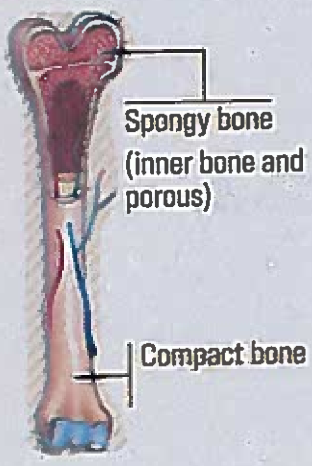
- Most hard of all connective tissue
- Covering of bone is called periosteum
- Haversian canals surround blood vessels and nerve cells throughout bones and communicate with bone cells
- Two types

Compact bone	Spongy bone/ cancellous bone
The outer layer of bones while	spongy or cancellous bone forms the inner layer of all bones
Compact bones are made of osteons	spongy bones are made of Trabeculae, filled with bone marrow

- **Bone cells:**

Osteoblasts	Osteocytes	Osteoclasts
Bone forming cells, causes mineralization via ALP.	These are mature bone cells, derived from osteoblasts	Dissolves bone/ resorption of bone causing bone remodeling.
	Lie within lacunae	Located in shallow grooves called Howship's lacunae





Layers of blood vessels

- Three layers
  - Tunica Intima → Inner most
  - Tunica Media → Middle layer
  - Tunica adventitia → outer layer

Skin

- Three layers
  - Epidermis
  - Dermis
  - Hypodermis
- Layers of epidermis: **C**ome **L**et's **G**et **S**un **B**urned)
  - **C**orneum, **L**ucidum, **G**ranulosum, **S**pinosum, **B**asale
- Location of Melanocytes in the skin is epidermis, and in epidermis it is located in Stratum basalis (the deepest layer of the five Epidermis layers)

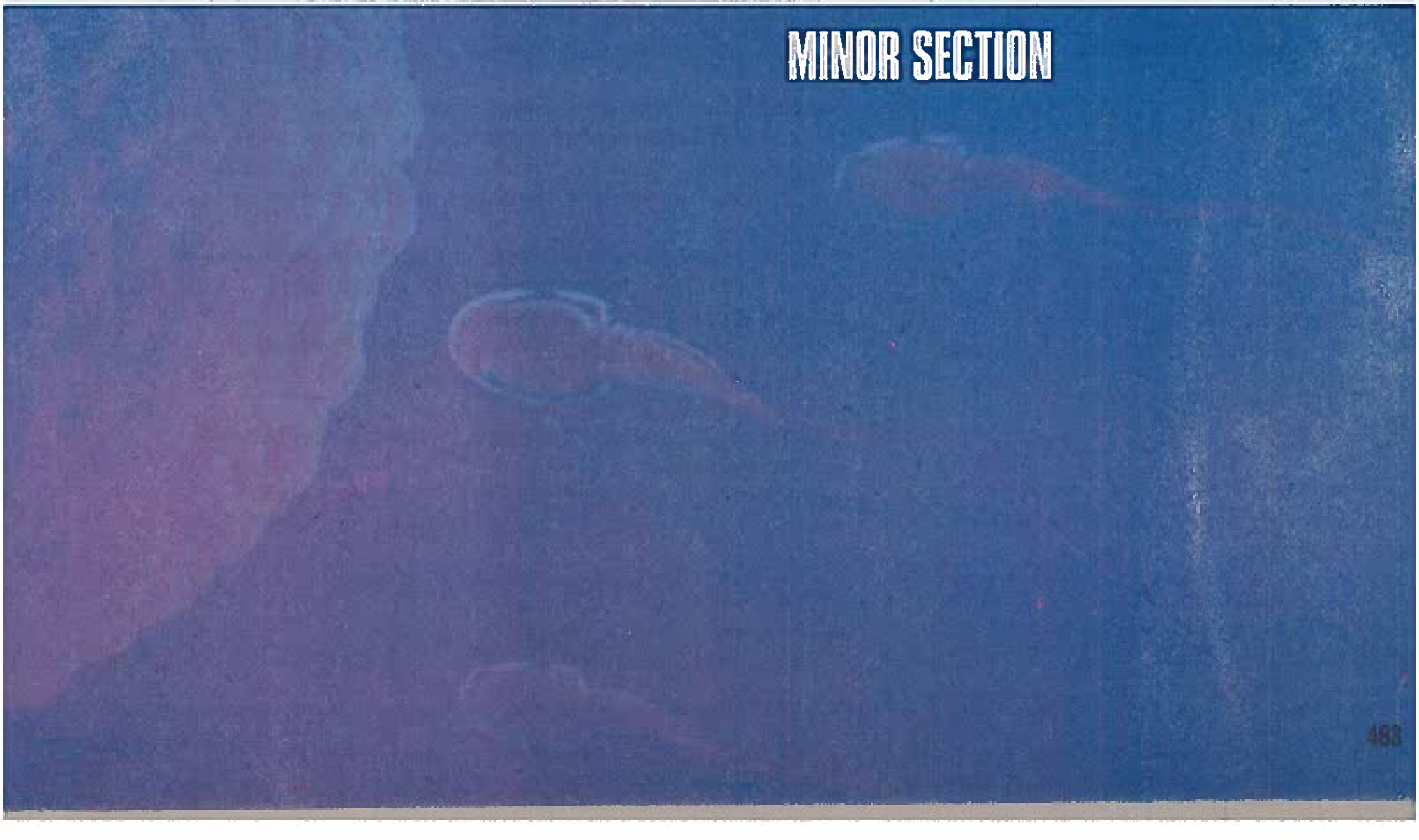
Wound Healing

Phases of healing	Characteristics
Inflammatory (up to 3 days after wound)	Clot formation, ↑vessel permeability and neutrophil migration into tissue.
Proliferative (day 3 till weeks after wound)	• Deposition of granulation tissue and type III collagen • Angiogenesis • Epithelial cell proliferation • Dissolution of clot, and • Wound contraction (mediated by myofibroblasts) ◦ Delayed wound healing in vitamin C deficiency and copper deficiency
Remodeling (1 week-6+ months after wound)	• Type III collagen replaced by type I collagen • ↑ strength of tissue ◦ Delayed wound healing in zinc deficiency

12

EMBRYOLOGY

MINOR SECTION



Chapter 1: Pre-Fertilization and Fertilization Events

Gametogenesis

Definition	• Gametogenesis means development of male and female germ cells or gamete.
Gametes	• Gametes are derived from primordial germ cells (PGC'S) that are formed in the **epiblast** during the 2nd week and that move to the wall of yolk sac
Oogenesis (Female Gametogenesis)	• The female germ cell is oocyte and its development is known as oogenesis. • Oogenesis ◦ Oogenesis refers to the sequence of events by which primitive germ cells call oogonia transforms into mature oocyte or ovum. ◦ Primordial Germ Cells (46,2N) from the wall of the yolk sac arrive in the ovary at week 6 of embryonic development and differentiate into oogonia (46,2N). ◦ Oogonia → enter meiosis- 1 & form primary oocytes. ◦ Primary oocytes → dormant in prophase (diplotene) of meiosis-1 until puberty. ◦ Primary oocyte → completes meiosis-1 to form a secondary oocyte during ovarian cycle. ◦ Secondary oocyte → remains arrested in metaphase of meiosis -2 until fertilization ◦ At fertilization, the secondary oocyte completes meiosis II to form a mature oocyte (23,1N) and a second polar body
Spermatogenesis (Male Gametogenesis)	• The male germ cells is spermatozoon and its development is known as spermatogenesis • Spermatogenesis: ◦ Spermatogenesis refers to the sequence of events by which primitive germ cells spermatogonia transforms into Sperm or spermatozoa. ◦ Primordial germ cells (46,2N) from the wall of the yolk sac arrive in the testes at week 6 of embryonic development and remain dormant until puberty. ◦ At puberty, primordial germ cells differentiate into type A spermatogonia. ◦ Type A spermatogonia undergo mitosis to form additional type A spermatogonia and type B spermatogonia. ◦ Type B spermatogonia divide by mitosis into **Primary spermatocytes** ◦ Primary spermatocytes undergoes first meiotic division to form two haploid **secondary spermatocytes** ◦ The secondary spermatocytes undergoes **2nd meiotic division to form 4 haploid spermatids** ◦ The spermatids undergo spermiogenesis to form **4 mature sperm**

Fertilization

Phase-1 Sperm Penetration Of Corona Radiata	•	Freshly ejaculated sperm are unable to fertilize they must undergo a period of modification called capacitation
	•	Capacitation:
	•	Glycoprotein coat and seminal plasma proteins are removed from the spermatozoon head which allow the sperm to move through corona cells
	•	Acrosome reaction:
	•	The acrosome of the sperm perforates the corona radiata by process called acrosome reaction
Phase-2 Sperm Binding And Penetration Of Zona Pellucida	•	Sperms comes in contact with plasma membrane of secondary oocyte, changes occur in zona pellucida termed as **zona reaction**
Phase-3 Fusion Of Sperm And Oocyte	•	As the sperm contacts, the secondary oocyte completes its second meiotic division and forms mature ovum.
	•	Male and female pronuclei formed which fuse to form zygote
Note	•	Fertilization occurs in the ampulla of uterine tube

Chapter 2:
Week 1st and 2nd of Development

1st Week

Clevage	• As the zygote passes to uterus it undergoes cleavage i.e. a series of rapid mitotic cell division • The new cells are known as Blastomeres • After several divsions mass of 16 blastomeres is formed known as Morula

3rd and 4th day	• Blastocyst formation:
	  • Three days after fertilization the morula enters the uterus
	  • Uterine fluid passes through the zona pellucida and fills the spaces
	  • These spaces form blastocyst activity and thus developing human is called Blastocyst.

5th day	• Degeneration of zona pelluicda → Blastocyst enlarges
6th day	• Initiaton of implantation • Differentiation of trophobalst • Differntitaes into cytotrophoblast (inner layer), and synctiotrophoblast (external layer)
7th day	• Formation of hypoblast → it gives rise to primitive endoderm

2nd Week

8th day	• **Fomration of Bilaminar Disc**
	  • Embryoblast differentiates into (Mnemonic **2** weeks = **2** layers)
	    • Epiblast = high columnar cells
	    • Hypoblast = small cuboidal cells
	• **Further differentiation of trophoblast:**
	  • Trophoblast → differentiates into
	    • Cytotrophoblasts (Mono-nucleated cells i.e mitotically active)
	    • Synsciotrophoblast (Multi-nucleated cells & no mitosis occurs)
	• **Formation of amniotic cavity**

9th day	• Formation of primary yolk sac or exocoelomic activity
10- 12th day	• Formation of extraembryonic mesoderm & extraembryonic coelom • the cells of yolk sac endoderm give rise to extraembryonic mesoderm • The extraembryonic mesoderm increases and isolated spaces appear in it which fuse to form a large cavity called extraembryonic coelom • Fomration of Yolk sac
13th day	• Formation of chorionic villi
Notes	• Epiblast contributes to the formation of amniotic cavity. • Hypoblast contributes to the formation of yolk sac • Epiblast and hypoblast fuse to form the prechordal plate which marks the future site of the mouth • hCG can be detected in maternal blood at **Day 8** or maternal urine at **Day 10** • Gestational trophoblastic neoplasia (GTN) or choriocarcinoma is a malignant tumor of the trophoblast. Elevated hCG levels are diagnostic. Mets spread to the liver and

Chapter 3:
Embryonic Period (Week 3-8)

- All major organ systems begin to develop during the embryonic period.
- By the end of embryonic period i.e. week 8 the embryo has a distinct human appearance.

Gastrulation
 	
Mnemonic= 3 weeks = 3 layers.
	• Is the formation of ectoderm, endoderm, mesoderm
	• **Ectoderm** gives rise to:
	  ◦ Neuroectoderm
	  ◦ Neural crest cells
	• **Mesoderm** gives rise to:
	  ◦ Paraxial mesoderm ⇨ Somites.
	  ◦ Intermediate mesoderm urogenital system.
	  ◦ Lateral mesoderm somatic layer and splanchnic layer.
	• Endoderm remains intact.
	• Ectoderm, endoderm and mesoderm forms a trilaminar embryonic disk.

Mesoderm (Somites)	• The Somites segment into the
	  ◦ Sclerotome ⇨ forms axial cartilage and bone.
	  ◦ Myotome ⇨ forms axial muscles.
	  ◦ Dermatome ⇨ forms dermis of skin.
	• The lateral mesoderm splits into somatic and splanchnic layer by the formation of intraembryonic coelom.
	• The somatic layer of the lateral mesoderm and the ectoderm forms the embryonic body wall or somatopleura.
	• The visceral layer of lateral mesoderm and endoderm forms the embryonic gut tube or splanchnopleura.
	• Sacrococcygeal Teratoma arises from the remnants of the primitive streak i.e. from the pluripotent cells of the primitive streak.

Notes	• The neurotransmitter serotonin (5HT) plays an important role in L/R axis determination. • Children whose mothers have been treated for depression with SSRIs have an increased risk of heart malformation • Decrease HCG level = spontaneous abortion, ectopic pregnancy. • Increase HCG level= multiple pregnancy, H. mole or GTN. • **Embryonic period i.e. from week 3- 8 is extremely susceptible to teratogens.**

Somites

- Somites develop from paraxial mesoderm

APPROX. AGE IN DAYS	NO. OF SOMITES	APPROX. AGE IN DATE	NO. OF SOMITES
20	1- 4	25	17-20
21	4- 7	26	20-23
22	7-10	27	23-26
23	10-13	28	26-29
24	13-17	30	34- 35

Germ Layers derivatives

Ectoderm	• Everything that makes you attractive:
	  · Skin (epidermis), hair, nails, Breasts, teeth enamel, lens, cornea etc.
	• Exocrine glands:
	  · Sweat, sebaceous, mammary, parotid, lacrimal, etc.
	• Nervous system: CNS and PNS
	  · From Neural Crest of Ectoderm
	    · Peripheral nervous system, Adrenal medulla, Melanocytes, Facial cartilage.
	• From Neural tube of Ectoderm
	    · Brain, Spinal cord, Posterior pituitary, Motor neurons, Retina, Anterior pituitary

Endoderm	• Lining of tube from nose, mouth and ear to anus and urethra and vagina • Internal organs: · Pharynx, thyroid, parathyroid, Trachea (epithelial parts), lungs, Stomach, Intestines (mucosal layers), colon (mucosal layers), liver, pancreas, bladder

Mesoderm	• Mnemonic **GONADS**
	  · **G**enitourinary and Renal
	  · **O**thers – Muscle, bone, connective tissue, serous lining of body cavities, cardiovascular system, parenchyma
	  · **N**otochord – **N**ucleus pulposus
	  · **A**drenal cortex
	  · **D**ura matter
	  · **S**pleen

Chapter 4:
Week 4-8 of Development

4th week Mnemonic= 4 weeks = 4 limbs and 4 heart chambers	• Closure of neuropores • *Pharyngeal arches becomes visible* • *Beginning of hemopoeisis in yolk sac* • Heart begins to beat. • Upper and lower limb buds begin to form. • Formation of otic and lens placodes
5th week	• Head and development of brain occurs rapidly, Face formed, Limb bud shows limbs • Stomach starts to rotate and midgut forms a loop
6th week	• The elbow and wrist regions are now identifiable • The foot plates have appeared and ankle regions become recognizable • The external acoustic meatus primodria of ear canals develop together with the external ears • Fetal cardiac activity visible by transvaginal ultrasound.
7th week	• Yolk sac is reduced to yolk stalk and limbs differentiate rapidly • Midgut herniation becomes prominent • By the end of 7th week ossification of bones of upper limb begins
8th week	• Fetal movements start • Facial features are distinct • Neck is established • The auricles of the external ears assume their final appearance • Digits of hands and feet separated along with regression of tail

Chapter 5:
Placenta, Amniotic Fluid and Umbilical Cord

Placenta

Main Function

- 1º site of nutrient and gas exchange between mother and fetus.

Fetal Component

- **Cytotrophoblast**
  - Inner layer of chorionic villi.
  - Cytotrophoblast makes Cells.
- **Syncytiotrophoblast**
  - oOuter layer of chorionic villi
  - Syncytiotrophoblast= Synthesizes and Secretes hormones, eg, hCG (structurally similar to LH; stimulates corpus luteum to secrete progesterone during first trimester).

Maternal Component

- **Decidua basalis**
  - Derived from endometrium

Placenta As Endocrine Organ

The placenta secretes:

- HCG
- Human placental lactogen (hPL)
- Estrogen, estradiol, estriol
- Progesterone

  Note: HCG stimulates progesterone production by corpus luteum. HPL induces lipolysis→ growth hormone of the fetus. Progesterone→maintains endometrium used by fetus for glucocorticoid, mineralocorticoid and testosterone synthesis.

Clinical Notes

- **Placenta Previa**
  - Is a condition when placenta attaches in the lower part of uterus, covering the internal Os.
  - It is the classic cause of 3rd trimester bleeding.
  - Ectopic pregnancy is the classic cause of bleeding in 1st trimester.
- **Placenta accreta**
  - oIs when placenta gets implanted in the myometrium
- **Placenta increta**
  - oIs when placenta gets implanted deep into the myometrium
- **Placenta percreta**
  - oIs when the placenta gets implanted through the wall of the uterus
- **Erythroblastosis Fetalis.**
  - The Rh factor is clinically important in pregnancy.
  - *If the mother is Rh-negative and the fetus is Rh-positive, the mother will produce Rh antibodies.*
  - *This situation will not affect the first pregnancy.*
  - *In the second pregnancy with an Rh-positive fetus, a hemolytic condition of red blood cells (RBCs) occurs, known as Rh-hemolytic disease of newborn (erythroblastosis fetalis).*

Amniotic fluid

Introduction	• Is maternally derived water that contains: electrolytes, carbohydrates, lipids • Amino acids, lipids, proteins (hormones, enzymes, α-fetoprotein), fetal urine, fetal feces (meconium), and fetal lung liquid (useful for lecithin/sphingomyelin [L/S] ratio measurement for lung maturity)
Oligohydramnios	• Is defined as amniotic fluid <400ml in late pregnancy due to inability of the fetus to excrete urine due to renal agenesis.
Polyhydramnios	• Is defines as amniotic fluid >2000ml in later pregnancy due to inability of fetus to swallow. This is commonly associate with maternal diabetes
Structures Passing Through Umbilical Ring	• 3 structures pass through the primitive umbilical ring: • Yolk sac (vitelline duct) • Connecting stalk • Allantois ◦ *The allantois aka urachus is not functional and degenerates to form the **median umbilical ligament** in the adult.*

Clinical Notes	• AFP is the fetal albumin produced by fetal hepatocytes. It is assessed in amniotic fluid and maternal serum between week 14 and 18 of gestation.
	  ◦ *Increased AFB: in neural tube defects i.e. Spina bifida, anencephaly. Omphalocele, oesophageal and duodenal atresia.*
	  ◦ *Decreased AFB: in down syndrome.*

Umbilical Cord

- The umbilical cord at term is:
  - Pearl white
  - 1-2cm in diameter
  - 50-60 cm long
  - **Contains the right and left umbilical arteries, carry deoxygenated blood from the fetus to the placenta.**
  - **Contains left umbilical vein, which carries oxygenated blood from the placenta to the fetus**
  - Mucus connective tissue (Wharton's jelly).

Chapter 6: Cardiovascular

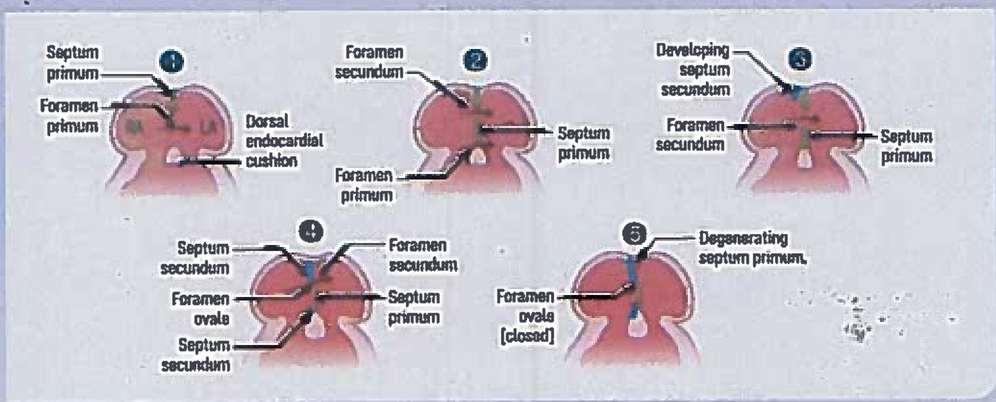
Primitive Heart Tube Dilatation

Embryonic Dilatation	Adult Structure
Truncus Arteriosus (T)	• Aorta • Pulmonary trunk
Bulbus Cordis (B)	• Smooth part of right ventricle **(conus arteriosus)** • Smooth part of left ventricle **(aortic vestibule)**
Primitive Ventricle (PV)	• Trabeculated part of right ventricle • Trabeculated part of left ventricle
Primitive Atrium (PA)	• Trabeculated part of right atrium • Trabeculated part of left atrium
Sinus Venosus (SV)	• Smooth part of right atrium **(sinus venarum)** • Coronary sinus • Oblique vein of left atrium

Septation of Chambers

Atria

1. Septum primum grows toward endocardial cushions, narrowing foramen primum.
2. Foramen secundum forms in septum primum (foramen primum disappears).
3. Septum secundum develops as foramen secundum maintains right-to-left shunt.
4. Septum secundum expands and covers most of the foramen secundum.
   The residual foramen is the foramen ovale.
5. Remaining portion of septum primum forms valve of foramen ovale.
6. (Not shown) Septum secundum and septum primum fuse to form the atrial septum.
7. (Not shown) Foramen Ovale usually closes soon after birth because of Inc. LA pressure.
8. Clinical Note
   - **Patent Foramen Ovale**
     Caused by failure of septum primum and septum secundum to fuse after birth



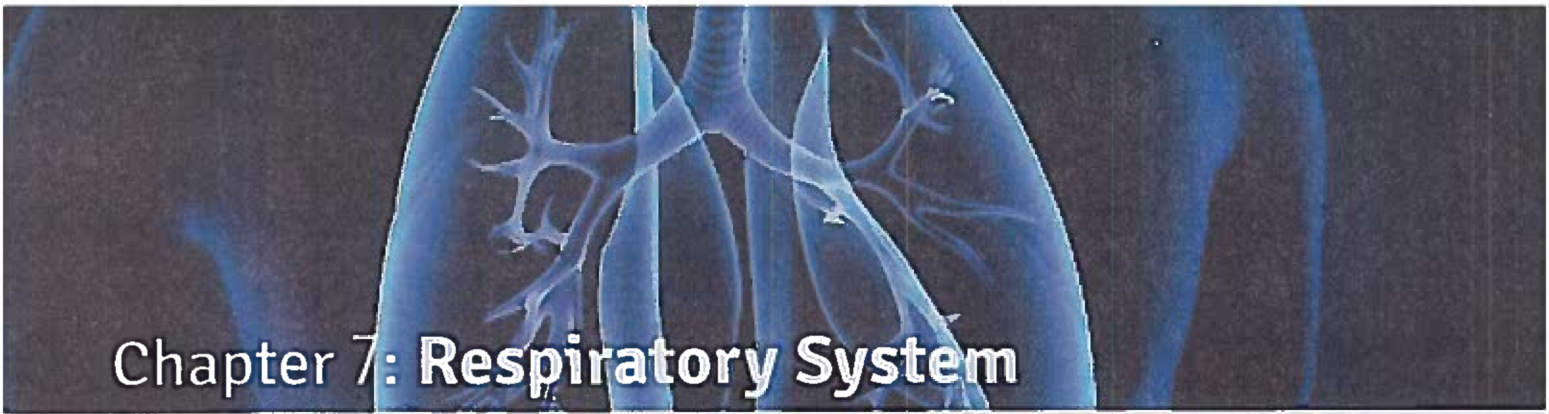
Ventricles	1. Muscular Interventricular septum forms, Opening is called interventricular foramen. 2. Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum, closing interventricular foramen. 3. Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum.

Fetal Circulation

- **Remember**
  - *Umbilical cord contains the right and left umbilical arteries, carry deoxygenated blood from the fetus to the placenta.*
  - *Contains left umbilical vein, which carries oxygenated blood from the placenta to the fetus*
- **Oxygenated blood**
  - Oxygenated blood enters IVC by Ductus venosus bypassing hepatic circulation
  - Oxygenated blood enters into right atrium and via foramen Ovale, bypasses right ventricle to enter left atrium then carried to left ventricle and is delivered via aorta to head and body.
  - After use deoxygenated blood is sent back to placenta via right and left umbilical arteries
- **Deoxygenated blood**
  - Deoxygenated blood from the SVC passes through the RA RV main pulmonary artery **Ductus arteriosus**
  - Descending aorta; shunt is due to high fetal pulmonary artery resistance (partly due to low O2 tension).
- **Circulation system changes and closure**
  - Circulatory system changes at birth infant takes a breath→↓resistance in pulmonary vasculature ↑venous
  - →↓return→↓left atrial pressure causes formane ovale to close
  - in O2 (from respiration) and↓in prostaglandins (from placental separation)→closure of ductus arteriosus
  - Clinical notes---failure of closure of Ductus arteriosus results in Patent Ductus arteriosus

Fetal-Postnatal Derivatives

AllaNtoisurachus	• *MediaN umbilical ligament*	*Urachus is part of allantoic duct between bladder and umbilicus.*
Ductus arteriosus	• vLigamentum arteriosum	
Ductus venosus	• Ligamentum venosum	
Foramen ovale	• Fossa ovalis	
Notochord	• *Fossa ovalis*	
UmbiLical arteries	• *vMediaL umbilical ligaments*	
Umbilical vein	• *Ligamentum teres hepatis (round ligament)*	*Contained in falciform ligament*



Chapter 7: Respiratory System

Development of Trachea

- The foregut is divided into the trachea ventrally and the esophagus dorsally by the tracheoesophageal folds, which fuse to form the tracheoesophageal septum.
- **Clinical notes:**
  - **Tracheoesophageal fistula** is an abnormal communication between the trachea and esophagus that results from improper division of the foregut by the tracheoesophageal septum.

Development of Lungs and Bronchi

- Occurs in five stages.
- Initial development includes development of lung bud from distal end of respiratory diverticulum during week 4.

Stage	Important	Notes
Embryonic (Weeks 4-7)	• At beginning of the 5th week lung bud forms two bronchial buds, which enlarges to form two main bronchi (Primary bronchi) • The right primary bronchus forms the secondary bronchus which itself has three lobes The left primary bronchus forms the secondary bronchus which itself has two lobes	Errors at this stage can lead to tracheoesophageal fistula.
Pseudoglandular Period (5th -16th Week)	• During this period branching continues to form terminal bronchioles	Respiration impossible, incompatible with life.
Canalicular Period (16th-24th Week)	• During this period each terminal bronchiole divides to form respiratory bronchioles (lining cuboidal cells) each of which in turn divides into 3-6 alveolar ducts	
Terminal Sac Period (24th Week Till Birth)	• By 24th week the terminal sac becomes lined by epithelial cells→type-I and type-II Pneumocytes develop	*Type-I Pneumocytes make part of blood air barrier* *Type-II Pneumocytes produce surfactant*
Alveolar (Week 36th – 8 Years)	• Lung development continues after birth until 8th year of postnatal life • The increase in size of lung after birth is due to increase in number of respiratory bronchioles and terminal sacs • Terminal sacs develop into mature alveolar ducts and alveoli	

Congenital Lung Malformations

Pulmonary Hypoplasia	• Poorly developed bronchial tree with abnormal histology. • Associated with congenital diaphragmatic hernia (usually left-sided), bilateral renal agenesis→ which causes an insufficient amount of amniotic fluid (oligohydramnios) to be produced.
Bronchogenic Cysts	• Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. • Discrete, round, sharply defined, fluid-filled densities on CXR. • Generally asymptomatic but can drain poorly, causing airway compression and/or recurrent respiratory infections.

Chapter 8: Renal & Urinary System

Development of Kidneys

- Three set of excretory organs develop in human embryo
    - 1. Pronephrons, 2. Mesonephrons, 3. Metanephrons
- At birth the kidneys are located in pelvis, but as the abdomen grows, they gradually come to lie in abdomen, attaining adult position by 9th week

Pronephrons	• 7-9 solid group cells, these are transitory, non-functional structures and entirely disappears by end of 4th week
Mesonephrons	• Functions as interim kidney for 1st trimester; later contributes to male genital system.
Metanephrons or Permanent kidneys	• Begins to develop early in 5th week, from the metanephric mesoderm • It develops from two sources ◦ The ureteric bud ▪ Ureteric bud arises as an outgrowth of mesonephric duct close to its entrance into cloaca ▪ Gives rise to ureter, pelvises, calyces, collecting ducts; fully canalized by 10th week ◦ Metanephrogenic cap ▪ It is a condensed mass of mesoderm ▪ Ureteric bud interacts with this tissue; interaction induces differentiation and formation of bowman's capsule, proximal and distal convoluted tubules and the loop of henle

Development of Urinary Bladder

- During the 4th and 7th week, urorectal septum divides the cloaca into anorectal region and primitive urogenital sinus
- The urinary bladder is formed from the upper portion of the urogenital sinus, which is continuous with the allantois.
- The lower ends of the mesonephric ducts become incorporated into the posterior wall of the bladder to form the trigone of the bladder.

Clinical Notes

Ectopic Kidney	• A condition in which kidneys remain in the pelvic cavity close to the common iliac artery
Horse Shoe Kidney	• In this condition the inferior pole of the two kidneys fuse • Horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. • Kidneys function normally. • Associated with hydronephrosis (e.g., ureteropelvic junction obstruction), renal stones, infection
Urachal Cyst Or Sinus	• It is remnant of allantois that persists and forms a cyst or sinus • It is formed along the midline from the umbilicus to the apex of urinary bladder Clinical it is associated with urine drainage from umbilicus

Potter Sequence (Syndrome)	• Potter sequence is the atypical physical appearance of a baby due to oligohydramnios experienced when in the uterus.
	• Clinical features: Mnemonic **POTTER**
	  ◦ **P**ulmonary hypoplasia (lack of amniotic fluid aspiration into fetal lungs)
	  ◦ **O**ligohydramnios (trigger)
	  ◦ **T**wisted face (low-set ears, retrognathia, flattened nose).
	  ◦ **T**wisted skin
	  ◦ **E**xtremity defects
	  ◦ **R**enal failure (in utero)---(bilateral renal agenesis)

Chapter 9: Gastrointestinal

Derivatives of Gut

Gut	• Derivatives	Arteries
Foregut	• Esophagus, stomach, upper part of duodenum upto opening of common bile duct	*celiac trunk*
Midgut	• Rest of duodenum, jejunum, ileum, appendix, caecum, ascending colon, and right 2/3rd of transverse colon	*superior mesenteric artery*
Hindgut	• Left 1/3rd of transverse colon, descending colon, proximal upper part of rectum	*inferior mesenteric artery*

Development of Gut from Esophagus till Colon

Esophagus	• The foregut is divided into the esophagus dorsally and the trachea ventrally by the tracheoesophageal folds, which fuse to form the tracheoesophageal septum
Stomach	• A fusiform dilatation forms in the foregut in week 4, which gives rise to the primitive stomach. • The primitive stomach rotates 90° clockwise around its longitudinal axis. • As a result of this clockwise rotation, the dorsal mesentery is carried to the left and eventually forms the greater omentum
Liver	• The endodermal lining of the foregut forms an outgrowth called the hepatic diverticulum (Liver bud) • The liver bud consists of rapidly developing cells columns of endodermal cells form the liver cords • Liver cords arrange themselves around the vitelline veins and umbilical veins form the hepatic sinusoids. • The liver bulges into the abdominal cavity, thereby stretching the septum transversum to form the ventral mesentery, consisting of the falciform ligament and the lesser omentum. • *The falciform ligament contains the left umbilical vein, which regresses after birth to form the ligamentum teres.* • The lesser omentum can be divided into the hepatogastric ligament and hepatoduodenal ligament. *The hepatoduodenal ligament contains the bile duct, portal vein, and hepatic artery (i.e., portal triad).* • Function:
Gall bladder and bile ducts	• The connection between the hepatic diverticulum and the foregut narrows to form the bile duct. • An outgrowth from the bile duct gives rise to the gallbladder rudiment and cystic duct.
Upper and lower duodenum	• The upper duodenum develops from the caudal portion of the foregut. • Lower Duodenum develops from the cranial-most part of the midgut.

Jejunum, Ileum, Cecum, Appendix, Ascending Colon, and Proximal Two-Thirds of Transverse Colon	• The midgut loop consists of a cranial limb and a caudal limb. • The cranial limb forms the jejunum and upper part of the ileum. • The caudal limb forms the cecal diverticulum, from which the cecum and appendix develop The rest of the caudal limb forms the lower part of the ileum, ascending colon, and proximal 2/3 of the transverse colon.

Midgut Development:

- 6th week—physiologic midgut herniates through umbilical ring
- Rotation of midgut
  - The midgut rotates by 90° around the axis by superior mesenteric artery and vitelline duct.
  - *During 10th week the herniated intestine loops returns to abdominal cavity, the midgut loop rotates counterclockwise by an additional **180°**, thus making rotation of loop through a total of **270° counterclockwise***

Clinical Notes

Gastroschisis	Omphalocele
A birth defect identified by incomplete closing of the abdominal wall, which causes the abdominal contents to bulge out	Persistent herniation of abdominal contents into umbilical cord, sealed by peritoneum
	

OMPHALOCELE
THE ABDOMINAL CONTENTS
ARE SEALED IN THE O.
THAT'S HOW YOU REMEMBER THAT
THEY ARE COVRED
BY THE PERITONEUM.

GASTROSCHISIS
THE ABDOMINAL CONTENTS
ARE COMING OUT OF THE G.
THAT'S HOW YOU REMMEBER THAT
THEY ARE NOT COVERED
BY THE PERITONEUM

Hypertrophic Pyloric Stenosis	• Most common cause of gastric outlet obstruction in infants
	• Clinical features:
	  ◦ *Nonbilious projectile vomiting at 2-6 weeks old.*
	  ◦ *Palpable olive-shaped mass in epigastric region*
	  ◦ *Visible peristaltic waves*

Hypertrophic Pyloric Stenosis	• Associated with exposure to **macrolides.** • *Results in hypokalemic hypochloremic metabolic alkalosis (2° to vomiting of gastric acid and subsequent volume contraction).* • Treatment is surgical incision (pyloromyotomy).
Esophageal Atresia	• it is a sporadic defect of GIT that results from incomplete division of the foregut into the trachea and the esophagus • Polyhydramnios in utero. Neonates drool, choke, and vomit with first feeding. • TEF allows air to enter stomach (visible on CXR).

Chapter 10: Head and Neck

Pharyngeal Apparatus

- Consists of the pharyngeal arches, pharyngeal pouches, pharyngeal grooves, and pharyngeal membranes, which are first observed in week 4 of development and give the embryo its distinctive appearance.
- Pharyngeal arch 5 and pharyngeal pouch 5 completely regress in the human.

Pharyngeal Arches Derivatives

Derivatives Of Pharyngeal Arches					
Pharyngeal Arches	**Artery**	**Nerve**	**Muscle**	**Ligament**	**Bones And Cartilage**
First Arch 1st arch is maximal.	Maxillary artery	Maxillary branch of trigeminal nerve Mandibular branch of trigeminal nerve, chorda tympani,	Muscles of Mastication, Mylohyoid, Anterior Belly of digastric.		*Maxilla* Zygomatic. Palatine bone. *Squamous part of temporal bone.* Meckel's cartilage. *Malleus, Incus.* *Mandibular process*
Second Arch **(Key word= S)**	Stapedial artery	***Facial nerve***	Muscles of facial expression. Posterior belly of digastric, Stylohyoid, Stapedius,	Stylohyoid Ligament	*Stapes.* *Stylohyoid* *Upper part of body of hyoid bone* *Lesser horn of hyoid bone.*
Third Arch **(Key word= pharyng)**	Internal Carotid artery. Common Carotid artery **Mnemonic=** C is 3rd letter of alphabet.	*Glossopharyngeal nerve.*	Stylo pharyngeus		*Greater horn of hyoid bone.* *Lower part of body of hyoid bone.*
Fourth arch	Right subclavian Arch of aorta	*Superior Laryngeal branch of vagus nerve*	Muscles of soft palate (except tensor veli palatine) *Cricothyroid. Cricopharyngeus*		Thyroid cartilage cricoid cartilage Arytenoid cartilage Corniculate Cartilage. Cuneiform Cartilage.

Sixth Arch	Ductus Arteriosus Right and left pulmonary arteries (proximal part)	*Recurrent laryngeal branch of vagus nerve*	*All intrinsic muscles of larynx **(except cricothyroid muscle)*** Skeletal muscle of esophagus.		Thyroid cartilage Cricoid cartilage Arytenoid cartilage Corniculate Cartilage cuneiform cartilage

Development of Thyroid Gland

- Thyroid diverticulum arises from floor of primitive pharynx and descends into neck.
- Connected to tongue by thyroglossal duct, which normally disappears.
- Foramen cecum is normal remnant of thyroglossal duct.
- Clinical notes:
    - *Thyroglossal duct cyst presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue* (vs persistent cervical sinus leading to branchial cleft cyst in lateral neck).

Development of Tongue

- The tongue consists of

Oral part (anterior 2/3rd of tongue)	• Forms from the **median tongue bud** and **two distal tongue buds** that develop in the floor of the pharynx associated with **pharyngeal arch 1.** • The distal tongue buds overgrow the median tongue bud and fuse in the midline, forming the **median sulcus.** • The oral part is characterized by **filiform papillae** (no taste buds), **fungiform papillae** (taste buds present), **foliate papillae** (taste buds present), and **circumvallate papillae** (taste buds present).
Pharyngeal part (posterior 1/3rd of tongue)	• Forms from the **copula** and **hypobranchial eminence** that develop in the floor of the pharynx associated with **pharyngeal arches** 2–4. • The hypobranchial eminence overgrows the copula, thereby eliminating any contribution of pharyngeal arch 2 in the formation of the definitive adult tongue. • The line of fusion between the oral and the pharyngeal parts of the tongue is indicated by the **terminal sulcus.** The pharyngeal part is characterized by the **lingual tonsil,** which forms along with the palatine tonsil and pharyngeal tonsil (adenoids), **Waldeyer's ring**.

Muscle of Tongue

- A middle fibrous septum divides the tongue into right and left halves
- Each half contains four intrinsic and four extrinsic muscles

Muscles	Intrinsic muscles	Extrinsic muscles
	• Superior longitudinal • Inferior longitudinal • Transverse • Vertical	• Genioglossus • Hyoglossus • Styloglossus • Palatoglossus

Nerve Supply of Tongue

Motor nerves	• All except palatoglossus muscle hypoglossal nerve • Palatoglossus muscle→accessory nerve through pharyngeal plexus.
Sensory nerves	• **Ant 2/3rd: (formed from 1st and 2nd branchial arches)** - General sensation: lingual nerve (mandibular branch) - Taste sensation: chorda tympani (facial nerve) • **Post 1/3rd: (formed from 3rd and 4th branchial arches)** - General and taste sensation: glossopharyngeal nerve

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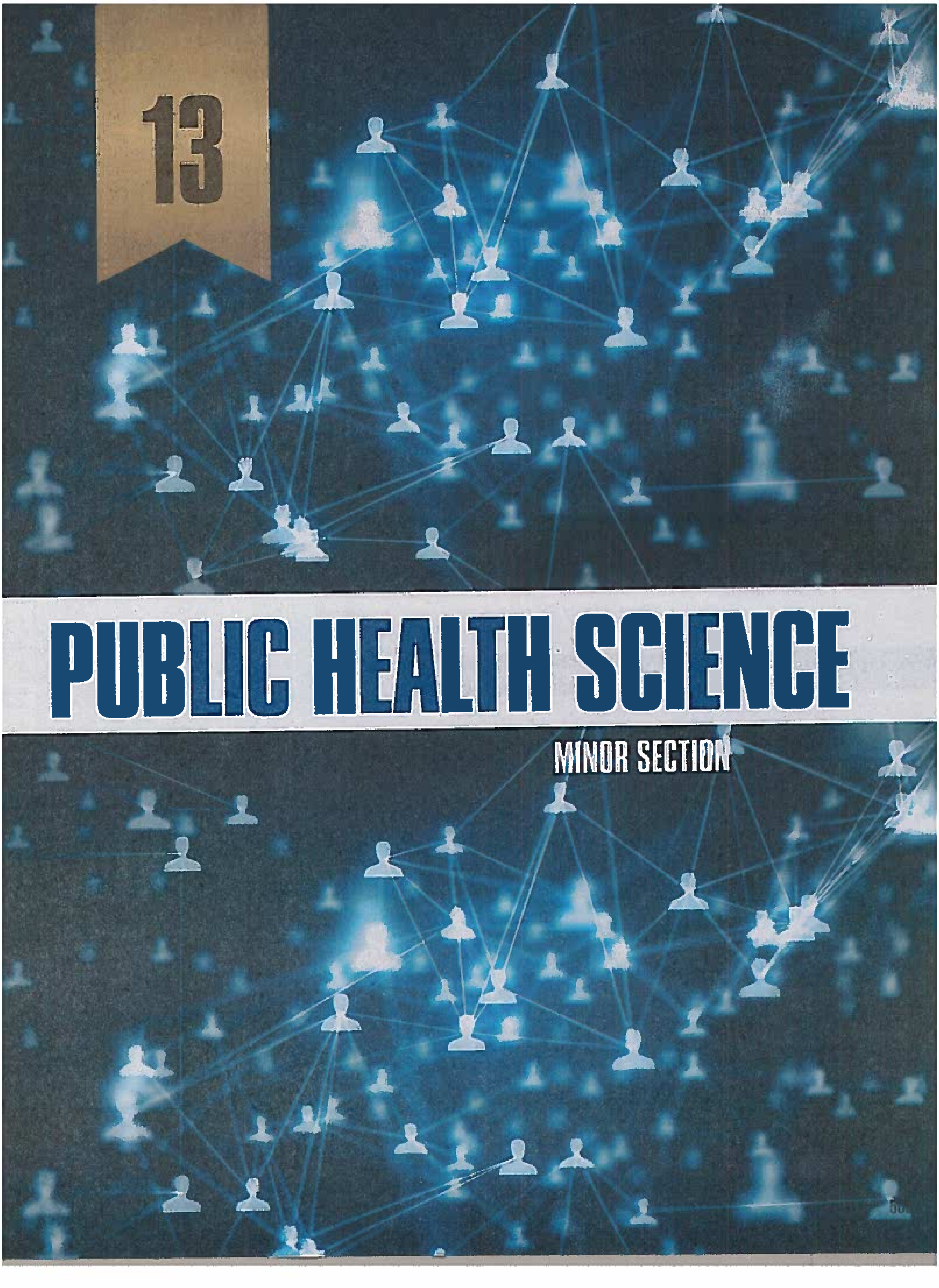

13

PUBLIC HEALTH SCIENCE

MINOR SECTION

Chapter :

Public Health Science

Incidence vs. Prevalence

Incidence	• *New cases (**incidents**) only at specified time period* • *Calculated as= no. of new cases/ no. of people at risk*
PrevAlence	• *Looks at All current cases at a point in time* • *Calculated as = no. of existing cases/ total no of people*

Positive and Negative Results

Positive Results	• True-positive (TP): Positive result in disease person • False-Positive (FP): Positive result in non-diseased person
Negative Results	• True-negative (TN) negative test in diseased person • False-negative (FN) negative test in non-diseased person

Positive and Negative Predictive Values

Positive Predictive Value:	• Likelihood that a person with a positive test result actually has the disease • Mathematically expressed as = $\frac{Tp}{Tp+Fp}$ x100 • Positive Predictive value is affected by Prevalence
Negative Predictive Value	• Likelihood that a person with a negative test result is actually free of the disease. • Mathematically expressed as= $\frac{TN}{TN+FN}$ x100

Sensitivity and Specificity

Sensitivity	• Sensitivity measures the extent to which a laboratory test is positive in patients. • Correctly identifies persons with the appropriate disease • Mathematically expressed as= $\frac{TP}{TP+FN}$ x100
Specificity	• Specificity measures the extent to which a laboratory test is negative in healthy persons • Correctly identifies persons who do not have the appropriate disease Mathematically expressed as= $\frac{TN}{TN+FN}$ x100

Sensitivity and specificity are independent of incidence and prevalence

Evaluation of Diagnostic test

	Disease ⊕	Disease ⊖
Test ⊕	TP	FP
Test ⊖	FN	TN
Also note that **Sensitivity=** $\frac{TP}{TP+FN}$		**Sensitivity=** $\frac{TN}{TN+FP}$

Example:

- A rapid finger-prick blood test to help diagnosis deep vein thrombosis is developed. Comparing the test to current standard techniques a study is done on 1.000 patients: from the below values, calculate the specificity of the new test?

	DVT present	DVT Absent
New test positive	200	100
New test negative	20	680

Solution:

- We know that
- **Specificity=** $\frac{TN}{TN+FP}$
- **So answer would be** $\frac{680}{680+100}$ = 680/780 ans

Observational Studies and Clinical Trials

Cross-Sectional Study	• *Collects data from group of people to asses frequency of disease and risk factors* • *It shows what's happening?*	Can show risk factor association with disease
Case-Control Study	• *Collects data from group of people with disease to compare with group without disease.* • *It shows, "What happened?"*	Patients with COPD had higher odds of a history of smoking than those without COPD
Cohort Study	• *Compares a group with a given exposure or risk factor to a group without such exposure.* • *vLooks to see if exposure or risk factor is associated with later development of disease.* • *vCan be prospective (asks, "Who will develop disease?") or* • *Retrospective (asks, "Who developed the disease [exposed vs. nonexposed]?").*	"Smokers had a higher risk of developing COPD than non-smokers"
Clinical Trial	• *Compares therapeutic benefits of 2 or more treatments, or of treatment and placebo.*	

Quantifying Risk

Definitions and formulas are based on the classic 2 × 2 or contingency table

	Disease +	Disease −
Risk factor or intervention +	a	b
Risk factor or intervention −	c	d

Odds Ratio (OR)

- Typically used in case-control studies.
- It represents the odds of an event (eg, disease) occurring giving a certain exposure (a/b) vs the odds of an event occurring in the absence of that exposure (c/d).
- Mathematically expressed as $= \frac{a/b}{c/d} = \frac{ad}{bc}$
- Example:
  - For example if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Achieved pain relief	Didn't achieve pain relief
Paracetamol	60	40	20
Placebo	90	30	60

- Solution:
  - The odds of achieving significant pain relief with paracetamol = 40 / 20 = 2
  - The odds of achieving significant pain relief with placebo = 30 / 60 = 0.5
  - Therefore the odds ratio = 2 / 0.5 = 4

Relative Risk (RR)

- Typically used in cohort studies.
- It represents the Risk of developing disease in the exposed group divided by risk in the unexposed group
- eg, if 21% of smokers develop lung cancer vs 1% of nonsmokers,
- So RR = 21/1 = 21.

Statistical Tests

t- test	• *Checks differences between means of 2 groups*	• Tea is meant for 2. • Example: comparing the mean blood pressure between men and women
ANOVA	• *Checks differences between means of 3 or more groups.*	• 3 words: ANalysis Of VAriance. vExample: comparing the mean blood pressure between members of 3 different ethnic groups

Chi-square (χ^2)	• *Checks differences between 2 or more percentages or proportions of **categorical** outcomes (not mean values).*	• Pronounce **Chi-tegorical.** • Example: comparing the percentage of members • of 3 different ethnic groups who have essential • hypertension

Mean, Median, Mode and Standard Deviation

- Examples- there are few numbers given calculate mean median and mode for it
  - Example 1: 13, 18, 13, 14, 13, 16, 14, 21, 13
  - Example 2: 8, 9, 10, 10, 10, 11, 11, 11, 12, 13

Mean	• Is equal to $\frac{\text{sum of values}}{\text{total numbers of values}}$ ✓ Example: 1 ▪ Mean $\frac{13+18+13+14+13+16+14+21+13}{9} = \frac{135}{9} = 15\text{ans}$ ✓ Example: 2 ▪ Mean $\frac{8+9+10+10+10+11+11+11+12+13}{10} = \frac{10.5}{10} = 15\text{ans}$
Median	• *Middle value of a list of data when arranged in ascending order as shown in example 1 below* • *But if there even are number of values, the median will be the average of the middle two values as shown in example 2 below* ✓ Example: 1 ▪ First arrange in ascending order 13, 13, 13, 13, 14, 14, 16, 18, 21 ▪ So median is the middle values which is 14 ✓ Example: 2 ▪ First arrange in ascending order 8, 9, 10, 10, 10, 11, 11, 11, 12, 13 ▪ Middle numbers are $\frac{10+11}{2} = 10.5\text{ans}$
Mode	• Most common value, if no number in the list is repeated, then there is no mode for the list. ✓ Example: 1 ▪ Mode is 13 ✓ Example: 2 ▪ Mode is = 10 and 11
Standard deviation (SD)	• *Variation from mean* • ***Variance = (SD)²*** ***SD=$\sqrt{\text{Variance}}$***

Pillars of Ethics

Autonomy	• The patient right to choose or refuse their treatment
Beneficence	• Always acting in the best interest of the patient
Nonmaleficence	• Above all—do not harm
Justice.	• To treat persons fairly and equitably. • This does not always imply equally (eg, triage).